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# RESPIRATORY CARE

A MONTHLY SCIENCE JOURNAL
47TH YEAR—ESTABLISHED 1956

## SPECIAL ISSUE

## LIQUID NEBULIZATION: EMERGING TECHNOLOGIES PART II

### CONFERENCE PROCEEDINGS

- Nebulizers That Force Pressurized Liquids Through Nozzles
- Nebulizers That Use a Vibrating Mesh or Plate with Multiple Apertures
- The Electrospray and Its Application to Targeted Drug Inhalation
- Smart Nebulizers
- Standardization Issues in Assessing Nebulizer Performance
- The Future of Nebulization
- Conference Summary

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### ACUTE RESPIRATORY DISTRESS SYNDROME (ARDS)

***NEW!*** ARDS: The Disease and its Management

Presents the four diagnostic criteria for ARDS and the six clinical risk factors that place patients at increased likelihood for developing ARDS. Teaches how to understand the implications of the lower and upper inflection points on the pressure-volume curve of the respiratory system in ARDS patients and instructs in the calculation of estimated required tidal volume. ITEM VC015-AV

### ASTHMA

Asthma: Managing the Disease

Takes a pro-active look at asthma from the perspective of disease management. You will learn the services necessary for an asthma disease management program, how to cost-effectively implement them and how to measure success through outcomes measurement. ITEM VC92-AV

***NEW!*** Education of the Patient with Asthma

Teaches how to ensure that patients understand the disease process of asthma and their care plan for effective disease management. Details what patient education materials are available, their content, where to find them and the best methods of presentation, including new terminologies, analogies and techniques. ITEM VC014-AV

Managing Asthma: An Update

Discover how to implement an asthma management program, what will work and how to determine if it is successful. Also, guidance is provided on how to analyze outcomes measurements. ITEM VC07-AV-

Pediatric Asthma in the ER

Because the prevalence of pediatric asthma has dramatically increased, the National Asthma Education and Prevention Program has created guidelines for management of pediatric asthma. This video discusses these guidelines as well as the role of care paths in the management of the disease. ITEM VC02-AV

### CHRONIC OBSTRUCATIVE PULMONARY DISEASE (COPD)

The Latest Word in the Treatment of COPD

Helps you understand what the barriers are to improved outcomes in COPD. Discusses the role of viral and bacterial infection in COPD exacerbation; the processes for clinical pathways development and the appropriate ventilator management strategies in severe COPD. ITEM VC96-AV

***NEW!*** Test Your Lungs, Know Your Numbers, Prevent Emphysema

Reviews the classic signs of COPD with an emphasis on emphysema and a discussion on the measures used to relieve symptoms and slow disease progression. Covers the importance of pulmonary function tests to determine VC, FFC and FEV1; also covers why getting patients to know their numbers is the key to early diagnosis and successful treatment. ITEM VC018-AV

### EMERGENCY CARE

Coping with the Pediatric Emergency

Provides an overview of assessing the pediatric patient. Includes discussion on differences in the anatomy and physiology of the pediatric respiratory system; recognition of the early signs of respiratory distress; the equipment and preparation needed to deal with respiratory emergencies and the priorities for management of pediatric respiratory emergencies. ITEM VC95-AV

Pediatric Asthma in the ER

Because the prevalence of pediatric asthma has dramatically increased, the National Asthma Education and Prevention Program has created guidelines for management of pediatric asthma. This video discusses these guidelines as well as the role of care paths in the management of the disease. ITEM VC02-AV

### MANAGEMENT, DEPARTMENT AND HOSPITAL

Cost-Effective Respiratory Care: You've Got to Change

Learn what the differences are between protocols and case management and how to implement these programs to generate cost savings. Learn how to identify where costs are avoided, where resources are conserved, and ensure that the correct care is delivered at the proper time. ITEM VC04-AV

### PULMONARY REHABILITATION

***NEW!*** Pulmonary Rehabilitation: Standard Care for Chronic Lung Disease Patients

Presentation details when to refer a patient for pulmonary rehabilitation and the four elements necessary for the successful operation of a rehabilitation service. Details how to prepare a treatment plan during assessment and how to modify it based on subsequent evaluations as well as how to incorporate rehabilitation techniques into routine bedside therapy sessions. ITEM VC012-AV

Pulmonary Rehabilitation: What You Need to Know

Learn the answers to: what is a sound pulmonary rehabilitation program, how to set up a rehab program; the role of assessment in developing an exercise prescription for patient rehab and the issues surrounding reimbursement and what the future holds. ITEM VC01-AV

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## PEDIATRICS

### Pediatric Asthma in the ER

Because the prevalence of pediatric asthma has dramatically increased, the National Asthma Education and Prevention Program has created guidelines for management of pediatric asthma. This video discusses these guidelines as well as the role of care paths in the management of the disease. ITEM VC02-AV

### Pediatric Ventilation: Kids Are Different

Receive instruction on the differences or the anatomy and physiology of the respiratory system between adults and children and how to mechanically ventilate the pediatric patient. Also, learn assessment and device selection. ITEM VC05-AV

### Theory and Application of Neonatal Ventilation: What, When, and Why

Evaluates neonates in need of ventilation, assessment and ventilator monitoring and how to recognize the neonate in respiratory failure. Also provided are instructions for minimizing iatrogenic lung damage, with a summary application of the new modes of ventilation and respiratory support for neonates. ITEM VC65-AV

## PHARMACOLOGY

### *NEW!* New Respiratory Drugs: What, When, and How?

Introduces new formulations such as racemic drug mixtures and single isomers and their effective duration and looks at how they lead to lower costs with improved patient responses. Learn the use of improved anticholinergics in the treatment of asthma patients and learn the uses and effects of inhaled anti-infective agents. Item VC016-AV

### Drugs, Medications and Delivery Devices of Importance in Respiratory Care

Aerosol therapy is delivered to nearly 80% of respiratory patients That is why there are a number of new medications in development for both local and systemic administration to these patients. Learn about these new medications, which delivery device to use, how to negotiate care plans and how to educate both patients and caregivers. ITEM VC03-AV

## PULMONARY FUNCTION TESTING AND DIAGNOSTIC EQUIPMENT

### Routine Pulmonary Function Testing: Doing it Right

Learn how to use bedside pulmonary function testing as a diagnostic tool and when its use is appropriate. Also, the viewer learns how to determine staff competence, quality assurance and testing accuracy. ITEM VC08-AV

### Waveform Analysis and Interpretation

Discusses the clinical applications of the primary waveforms, the general kinds of information they provide and how to use them to adjust the patient-ventilator interface. ITEM VC72-AV

## PHYSIOLOGY AND HEMODYNAMICS

### Hemodynamic Monitoring

Identifies the different forms of invasive and noninvasive hemodynamic monitoring, their main complications and appropriate levels. Discusses how positive end-expiratory pressure and other therapies affect parameters. Item VC22-AV

*Comprehensive, easy-to-use programs include advice from respiratory care's top experts.*

## VENTILATORS AND VENTILATOR PATIENT MANAGEMENT

### *NEW!* Invasive Ventilation: The Latest Word

Learn how proper ventilator management precludes inflicting harm on the patient and why the clinician must understand the function and mechanics of newer mechanical ventilators. Also learn how reducing the patient's work of breathing is essential in reducing the additional load on ventilatory musculature and why reinflating lungs and enhancing the functional area of the lung demand extraordinary means. Item VC017-AV

### Managing the Mechanically Ventilated Patient: Chest Tubes, Aerosols, Endotracheal Tubes

Teaches how endotracheal tubes impose work and create infection risk, the efficacy of various systems, the indications, positioning issues and drainage issues for chest tubes. ITEM VC71-AV

### *NEW!* Noninvasive Ventilation: The Latest Word

Learn how to avoid intubation in the acutely ill patient through identification of patients most likely to benefit from noninvasive ventilation. Learn selection and proper fit of full masks or nasal masks and how to select the proper ventilator based on the patient's condition and desired outcomes. Also learn when to make adjustments to achieve the goals of unloading respiratory muscles and achieving good patient ventilator synchrony ITEM VC013-AV

### Pediatric Ventilation: Kids Are Different

Instructs on the differences in the anatomy and physiology of the respiratory system between adults and children and how to mechanically ventilate the pediatric patient. Also, learn assessment and device selection. ITEM VC05-AV

### PEEP: The State of the Art

Discusses current applications of positive end-expiratory pressure (PEEP); the relationship of PEEP to end-respiratory lung volume and its consequences for gas exchange in acute lung injury and how PEEP can prevent it; the benefits of adding PEEP in the setting of severe airflow obstruction and dynamic hyperinflation; and the selection of PEEP and tidal volume for ventilation of the injured lung ITEM VC97-AV

### *NEW!* Taking the Mystery Out of Weaning the Pediatric Patient from the Ventilator

Learn the weaning process and how to recognize critical events in weaning a pediatric patient Also teaches the physiological differences between the adult and pediatric patient and why weaning of the pediatric patient is different. Item VC011-AV

### Theory and Application of Neonatal Ventilation: What, When, and Why

Evaluates neonates in need of ventilation, assessment and ventilator monitoring and how to recognize the neonate in respiratory failure. Also provided are instructions for minimizing iatrogenic lung damage. Item VC65-AV

### Ventilators and Their Management

Discusses the efficacy of the latest mechanical ventilation technology and techniques over-distension lung injury, PEEP in the avoidance of lung injury; strategy to improve patient-ventilator synchrony and the role of the ventilator in ventilator-associated lung injury ITEM VC93-AV

### Waveform Analysis and Interpretation

Discusses the clinical applications of the primary waveforms, the general kinds of information they provide and how to use them to adjust the patient-ventilator interface. Item VC72-AV

### What Matters in Respiratory Monitoring: What Goes and What Stays

Details the monitoring devices available for managing the patient and which is appropriate. Also learn about displays and graphics on ventilators and covers what information is essential in the assessment of the patient ITEM VC06-AV

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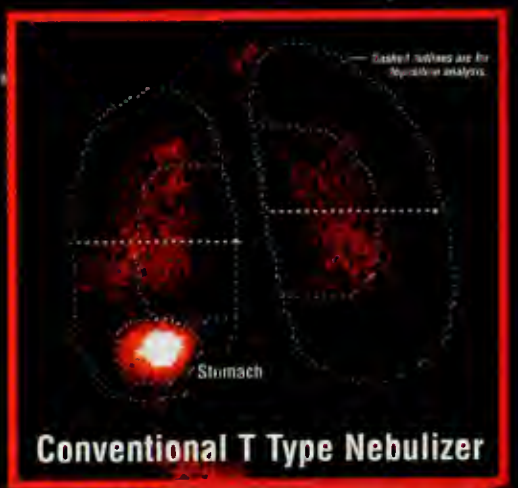


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*Photo Source: *Predicting Lung Deposition with a Cascade Impactor*, Sangwan S Hull F Condos R Smaldone GC *Journal of Aerosol Medicine* 2001, 14(3):421

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Director of Govt Affairs
Jill Eicher
1225 King St, Second Floor
Alexandria VA 22314
(703) 548-8538 Fax (703) 548-8499
eicher@aarc.org

Director of State Govt Affairs
Cheryl West MHA
8630 Braeswood Pt. #2
Colorado Springs, CO 80920
(719) 535-9970 west@aarc.org

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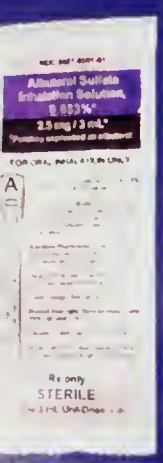


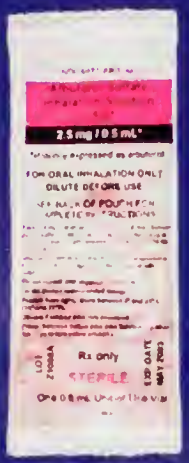


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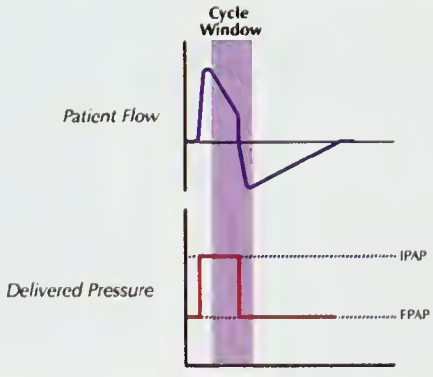


Normal Lungs

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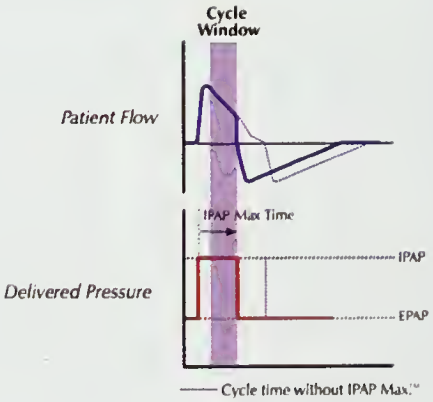
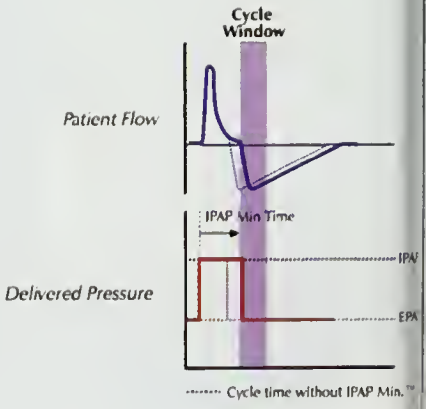



Obstructive Disease

(High Airway Resistance-Device cycles within Cycle Window at IPAP Max Time)




Restrictive Disease

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**Editorials, Commentaries, and Reviews to Note**

**Pharmacologic Therapy for Nicotine Addiction** (editorial)—DeGraff AC Jr. Chest 2002 Aug;122(2):392-394.

**Magnesium Treatment for Asthma: Where Do We Stand?** (editorial)—Noppen M. Chest 2002 Aug;122(2):396-398.

**Hospitals vs Merchants of Nicotine** (editorial)—Soffer A. Chest 2002 Aug;122(2):391-392.

**Do Nurses Do It Better?** (editorial)—Rafferty S, Elborn JS. Thorax 2002 Aug;57(8):659-660.

**Invited Editorial on "The Alcohol Breath Test"**—Hlastala MP. J Appl Physiol 2002 Aug;93(2):405-406.

**Homing in on the Asthma Gene** (comment)—Sandford A, Pare P. Lancet 2002 Aug 10;360(9331):422-423.

**What Is Cystic Fibrosis?** (editorial)—Knowles MR, Durie PR. N Engl J Med 2002 Aug 8;347(6):439-442.

**The Pulmonary Physician in Critical Care. 8: Ventilatory Management of ALI/ARDS**—Cordingley JJ, Keogh BF. Thorax 2002 Aug;57(8):729-734.

**Chronic Obstructive Pulmonary Disease. 1: Susceptibility Factors for COPD the Genotype-Environment Interaction**—Sandford AJ, Silverman EK. Thorax 2002 Aug;57(8):736-741.

**"CF Asthma": What Is It and What Do We Do About It?**—Balfour-Lynn IM, Elborn JS. Thorax 2002 Aug;57(8):742-748.

**The Costs of Exacerbations in Chronic Obstructive Pulmonary Disease (COPD)**—Andersson F, Borg S, Jansson SA, Jonsson AC, Ericsson Å, Prütz C, et al. Respir Med 2002 Sep;96(9):700-708.

Exacerbations are the key drivers in the costs of chronic obstructive pulmonary disease (COPD). The objective was to examine the costs of COPD exacerbations in relation to differing degrees of severity of exacerbations and of COPD. We identified 202 subjects with COPD, defined according to the BTS and ERS criteria. Exacerbations were divided into mild (self-managed), mild/moderate (telephone contact with a health-care centre and/or the use of antibiotics/systemic corticosteroids), moderate (health-care centre visits) and severe (emergency care visit or hospital admission). Exacerbations were identified by sending the subjects a letter inquiring whether they had any additional respiratory problems or influenza the previous winter. At least one exacerbation was reported by 61 subjects, who were then interviewed about resource use for these events. The average health-care costs per exacerbation were SEK 120 (95% C=39-246), SEK 354 (252-475), SEK 2111 (1673-2612) and SEK 21852 (14436-29825) for mild, mild/moderate, moderate and severe exacerbations, respectively. Subjects with impaired lung function experienced more severe exacerbations, which was also reflected in the cost of exacerbations per severity of the disease during the 4 1/2 month study period (ranging from SEK 224 for mild to SEK 13708 for severe cases, median SEK 940). Exacerbations account for 35-45% of the total per capita health-care costs for COPD. In conclusion, costs varied considerably with the severity of the exacerbation as well as with the severity of COPD. The prevention of moderate-to-severe exacerbations could be very cost-effective and improve the quality of life.

**Home Visiting by Paraprofessionals and by Nurses: A Randomized, Controlled Trial**—Olds DL, Robinson J, O'Brien R, Luckey DW, Pettitt LM, Henderson CR Jr, et al. Pediatrics 2002 Sep;110(3):486-496.

OBJECTIVE: To examine the effectiveness of home visiting by paraprofessionals and by nurses as separate means of improving maternal and child health when both types of visitors are trained in a program model that has demonstrated effectiveness when delivered by nurses. METHODS: A randomized, controlled trial was conducted in public- and private-care settings in Denver, Colorado. One thousand one hundred seventy-eight consecutive pregnant women with no previous live births who were eligible for Medicaid or who had no private health insurance were invited to participate. Seven hundred thirty-five women were randomized to control, paraprofessional, or nurse conditions. Nurses completed an average of 6.5 home visits during pregnancy and 21 visits from birth to the children's second birthdays. Paraprofessionals completed an average of 6.3 home visits during pregnancy and 16 visits from birth to the children's second birthdays. The main outcomes consisted of changes in women's urine cotinine over the course of pregnancy; women's use of ancillary services during pregnancy; subsequent pregnancies and births, educational achievement, workforce participation, and use of welfare; mother-infant responsive interaction; families' home environments; infants' emotional vulnerability in response to fear stimuli and low emotional vitality in response to joy and anger stimuli; and children's language and mental development, temperament, and behavioral problems. RESULTS: Paraprofessional-visited mother-child pairs in which the mother had low psychological resources interacted with one another more responsively than their control-group counterparts (99.45 vs 97.54

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standard score points). There were no other statistically significant paraprofessional effects. In contrast to their control-group counterparts, nurse-visited smokers had greater reductions in cotinine levels from intake to the end of pregnancy (259.0 vs 12.32 ng/mL); by the study child's second birthday, women visited by nurses had fewer subsequent pregnancies (29% vs 41%) and births (12% vs 19%); they delayed subsequent pregnancies for longer intervals; and during the second year after the birth of their first child, they worked more than women in the control group (6.83 vs 5.65 months). Nurse-visited mother-child pairs interacted with one another more responsively than those in the control group (100.31 vs 98.99 standard score points). At 6 months of age, nurse-visited infants, in contrast to their control-group counterparts, were less likely to exhibit emotional vulnerability in response to fear stimuli (16% vs 25%) and nurse-visited infants born to women with low psychological resources were less likely to exhibit low emotional vitality in response to joy and anger stimuli (24% vs 40% and 13% vs 33%). At 21 months, nurse-visited children born to women with low psychological resources were less likely to exhibit language delays (7% vs 18%); and at 24 months, they exhibited superior mental development (90.18 vs 86.20 Mental Development Index scores) than their control-group counterparts. There were no statistically significant program effects for the nurses on women's use of ancillary prenatal services, educational achievement, use of welfare, or their children's temperament or behavior problems. For most outcomes on which either visitor produced significant effects, the paraprofessionals typically had effects that were about half the size of those produced by nurses. CONCLUSIONS: When trained in a model program of prenatal and infancy home visiting, paraprofessionals produced small effects that rarely achieved statistical or clinical significance; the absence of statistical significance for some outcomes is probably attributable to limited statistical power to detect small effects. Nurses produced significant effects on a wide range of maternal and child outcomes.

**Effects of Volume-Guaranteed Synchronized Intermittent Mandatory Ventilation in Preterm Infants Recovering from Respiratory Failure**—Herrera CM, Gerhardt T, Claure N, Everett R, Musante G, Thomas C, Bancalari E. Pediatrics 2002 Sep;110(3):529-533.

OBJECTIVE: Volume guarantee (synchronized intermittent mandatory ventilation [SIMV]+VG) is a novel mode of SIMV for automatic adjustment of the peak inspiratory pressure to ensure a minimum set mechanical tidal volume ($V_{T\ mech}$). The objective of this study was to compare the effects of SIMV+VG with conventional SIMV on ventilation and gas exchange in a group of very low birth weight infants recovering from acute respiratory failure. METHODS: Nine infants were initially studied during 2 consecutive 60-minute ventilatory modalities of conventional SIMV (ventilator settings by clinical team) and SIMV+VG 4.5 ($V_{T\ mech}$ set at 4.5 mL/kg) in random order. Eight additional infants were studied during the same ventilatory modalities plus 1 additional epoch consisting of SIMV+VG 3.0 ($V_{T\ mech}$ set at 3.0 mL/kg). RESULTS: Peak inspiratory pressure was significantly lower during SIMV+VG 3.0. Mean airway pressure, $V_{T\ mech}$, number of large $V_{T\ mech}$ (>7 mL/kg), and mechanical minute ventilation ($\dot{V}_E$) were reduced during SIMV+VG 4.5 compared with SIMV and were further reduced during SIMV+VG 3.0. Spontaneous $\dot{V}_E$ increased during SIMV+VG 4.5 and was even higher during SIMV+VG 3.0. The resulting total $\dot{V}_E$ was higher during both SIMV+VG modes compared with SIMV. Arterial oxygen saturation by pulse oximetry, transcutaneous carbon dioxide tension, and fraction of inspired oxygen did not differ significantly, although transcutaneous carbon dioxide tension increased slightly during SIMV+VG 3.0. CONCLUSIONS: The short-term use of SIMV+VG resulted in automatic weaning of the mechanical support and enhancement of the spontaneous respiratory effort while maintaining gas exchange relatively unchanged in comparison to conventional SIMV.

**Comparison of Effects of Strength and Endurance Training in Patients with Chronic Obstructive Pulmonary Disease**—Ortega F, Toral J, Cejudo P, Villagomez R, Sanchez H, Castillo J, Montemayor T. Am J Respir Crit Care Med 2002 Sep 1;166(5):669-674.

We determined the effect of different exercise training modalities in patients with chronic obstructive pulmonary disease, including strength training (n = 17), endurance training (n = 16), and combined strength and endurance (n = 14) (half of the endurance and half of the strengthening exercises). Data were compared at baseline, the end of the 12-week exercise-training program, and 12 weeks later. Improvement in the walking distance was only significant in the strength group. Increases in submaximal exercise capacity for the endurance group were significantly higher than those observed in the strength group but were of similar magnitude than those in the combined training modality, which in turn were significantly higher than for the strength group. Increases in the strength of the muscle groups measured in five weight lifting exercises were significantly higher in the strength group than in the endurance group but were of similar magnitude than in the combined training group, which again showed significantly higher increases than subjects in the endurance group. Any training modality showed significant improvements of the breathlessness score and the dyspnea dimension of the chronic respiratory questionnaire. In conclusion, the combination of strength and endurance training seems an adequate training strategy for chronic obstructive pulmonary disease patients.

**Oral Appliance Therapy Improves Symptoms in Obstructive Sleep Apnea: A Randomized, Controlled Trial**—Gotsopoulos H, Chen C, Qian J, Cistulli PA. Am J Respir Crit Care Med 2002 Sep 1;166(5):743-748.

The aim of this study was to evaluate the effect of a mandibular advancement splint (MAS) on daytime sleepiness and a range of other symptoms in obstructive sleep apnea (OSA). Using a randomized crossover design, patients received 4 weeks of treatment with MAS and a control device (inactive oral appliance), with an intervening 1-week washout. At the end of each treatment period, patients were reassessed by questionnaire, polysomnography, and multiple sleep latency test. Fifty-nine men and 14 women with a mean (± SD) age of 48 ± 11 years and proven OSA experienced a significantly improved mean (± SEM) sleep latency on the multiple sleep latency test (10.3 ± 0.5 versus 9.1 ± 0.5 minutes, $p = 0.01$) and Epworth sleepiness scale score (7 ± 1 versus 9 ± 1, $p < 0.0001$) with the MAS compared with the control device after 4 weeks. The proportion of patients with normal subjective sleepiness was significantly higher with the MAS than with the control device (82 versus 62%, $p < 0.01$), but this was not so for objective sleepiness (48 versus 34%, $p = 0.08$). Other OSA symptoms were controlled in significantly more patients with the MAS than with the control device. MAS therapy improves a range of symptoms associated with OSA.

**Are Tidal Volume Measurements in Neonatal Pressure-Controlled Ventilation Accurate?**—Chow LC, Vanderhal A, Raber J, Sola A. Pediatr Pulmonol 2002 Sep;34(3):196-202.

Bedside pulmonary mechanics monitors (PMM) have become useful in ventilatory management in neonates. These monitors are used more frequently due to recent improvements in data-processing capabilities. PMM devices are often part of the ventilator or are separate units. The accuracy and reliability of these systems have not been carefully evaluated.We compared a single ventilatory parameter, tidal volume ($V_t$), as measured by several systems. We looked at two freestanding PMMs: the Ventrak Respiratory Monitoring System (Novametrix, Wallingford, CT) and the Bicore CP-100 Neonatal Pulmonary Monitor (Allied Health Care Products, Riverside, CA), and three ventilators with built-

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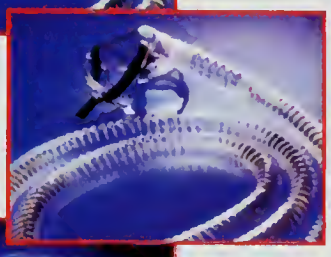

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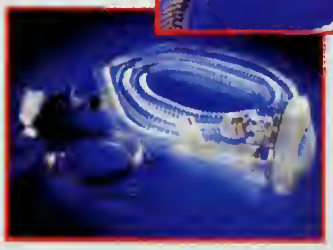

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in PMM: the VIP Bird Ventilator (Bird Products Corp., Palm Springs, CA), Siemens Servo 300A (Siemens-Elema AB, Solna, Sweden), and Dräger Babylog 8000 (Dräger, Inc., Chantilly, VA). A calibrated syringe (Hans Rudolph, Inc., Kansas City, MO) was used to deliver tidal volumes of 4, 10, and 20 mL to each ventilator system coupled with a freestanding PMM. After achieving steady state, six consecutive $V_t$ readings were taken simultaneously from the freestanding PMM and each ventilator. In a second portion of the bench study, we used pressure-control ventilation and measured exhaled tidal volume ($V_{te}$) while ventilating a Bear Test Lung with the same three ventilators. We adjusted peak inspiratory pressure (PIP) under controlled conditions to achieve the three different targeted tidal volumes on the paired freestanding PMM. Again, six $V_{te}$ measurements were recorded for each tidal volume. Means and standard deviations were calculated.The percentage difference in measurement of $V_t$ delivered by calibrated syringe varied greatly, with the greatest discrepancy seen in the smallest tidal volumes, by up to 28%. In pressure control mode, $V_{te}$ as measured by the Siemens was significantly overestimated by 20-95%, with the biggest discrepancy at the smallest $V_{te}$, particularly when paired with the Bicore PMM. $V_{te}$, as measured by the VIP Bird and Dräger paired with the Ventrak PMM, had a tendency to underestimate $V_t$ by up to 25% at the smallest $V_{te}$. However, when paired with the Bicore PMM, these same two ventilators read over target by up to 18%.Under controlled laboratory conditions, we demonstrated that true delivered $V_{te}$, as measured by the three ventilators and two freestanding PMM, differed markedly. In general, decreasing dynamic compliance of the tubing was not associated with greater inaccuracy in $V_{te}$ measurements.

**High-Frequency Oscillatory Ventilation for the Prevention of Chronic Lung Disease of Prematurity**—Johnson AH, Peacock JL, Greenough A, Marlow N, Limb ES, Marston L, Calvert SA; United Kingdom Oscillation Study Group. N Engl J Med 2002 Aug 29;347(9):633-642.

BACKGROUND: There remains uncertainty concerning the safety and efficacy of high-frequency oscillatory ventilation as compared with those of conventional ventilation for the respiratory support of very preterm infants. We conducted a multicenter trial to determine whether early intervention with high-frequency oscillatory ventilation reduced mortality and the incidence of chronic lung disease among newborns with a gestational age of 28 weeks or less. METHODS: We randomly assigned preterm infants with a gestational age of 23 to 28 weeks to either conventional ventilation or high-frequency oscillatory ventilation within one hour after birth. Randomization was stratified according to center and gestational age (23 to 25 weeks or 26 to 28 weeks). RESULTS: A total of 400 infants were assigned to high-frequency oscillatory ventilation, and 397 were assigned to conventional ventilation. The composite primary outcome (death or chronic lung disease, diagnosed at 36 weeks of postmenstrual age) occurred in 66 percent of the infants assigned to receive high-frequency oscillatory ventilation and 68 percent of those in the conventional-ventilation group (relative risk in the group assigned to high-frequency oscillatory ventilation, 0.98; 95 percent confidence interval, 0.89 to 1.08). Similar proportions of infants died or had chronic lung disease in each gestational-age group. In both treatment groups treatment failure occurred in 10 percent of infants (relative risk in the group assigned to high-frequency oscillatory ventilation, 0.99; 95 percent confi-

dence interval, 0.66 to 1.50). There were no significant differences between the groups in a range of other secondary outcome measures, including serious brain injury and air leak. CONCLUSIONS: The results obtained with high-frequency oscillatory ventilation and conventional ventilation do not differ significantly in the early treatment of respiratory disease in very preterm infants. Assessment of long-term effects will require additional follow-up.

**High-Frequency Oscillatory Ventilation Versus Conventional Mechanical Ventilation for Very-Low-Birth-Weight Infants**—Courtney SE, Durand DJ, Asselin JM, Hudak ML, Aschner JL, Shoemaker CT; Neonatal Ventilation Study Group. N Engl J Med 2002 Aug 29;347(9):643-652.

BACKGROUND: The efficacy and safety of early high-frequeocy oscillatory ventilation as compared with conventioual synchronized intermittent mandatory ventilation for the treatment of infants with very low birth weight have not been established. METHODS: We conducted a raodomized, multicenter clinical trial to determine whether infants treated with early high-frequency oscillatory ventilation were more likely than infants treated with syochrooized intermittent mandatory ventilation to be alive without requiring supplemental oxygeo at 36 weeks of postmenstrual age. Eligible infants weighed 601 to 1200 g at birth, were less thao four hours of age, had received one dose of surfactant, and required ventilation with a mean airway pressure of at least 6 cm of water and a fraction of inspired oxygen of at least 0.25. Infants were stratified according to birth weight and exposure to prenatal corticosteroids and then raodomly assigoed to high-frequency oscillatory ventilation or synchronized intermittent mandatory ventilation. Ventilation was managed according to protocols designed to optimize lung ioflatioo and blood gas values. RESULTS: Five hundred infants were enrolled in the study. Infants randomly assigned to high-frequency oscillatory ventilation were successfully extubated earlier than infants assigned to synchronized intermittent mandatory ventilatioo (p<0.001). Of infants assigned to high-frequency oscillatory ventilation, 56 percent were alive without a need for supplemental oxygen at 36 weeks of postmenstrual age, as compared with 47 percent of those receiving synchronized intermittent mandatory ventilation (p=0.046). There was oo difference between the groups in the risk of intracranial hemorrhage, cystic periventricular leukomalacia, or other complications. CONCLUSIONS: There was a small but significant benefit of high-frequeocy oscillatory ventilation in terms of the pulmonary outcome for very-low-birth-weight infants without an increase in the occurrence of other complications of premature birth.

**Dead-Space Reduction and Tracheal Pressure Measurements Using a Coaxial Inner Tube in an Endotracheal Tube**—Lethvall S, Sondergaard S, Karason S, Lundin S, Stenqvist O. Intensive Care Med 2002 Aug;28(8):1042-1048.

OBJECTIVE. To evaluate the effects on $CO_2$ washout of the coaxial double lumen tube (DLT) as compared to a standard endotracheal tube (ETT) and tracheal gas insufflation (TGI). Precision of tracheal pressure monitoring through the DLT and safety issues, including intrinsic PEEP (PEEPi) formation during DLT ventilation, were also evaluated. DESIGN. Lung model study. SETTING. University research laboratory. MEASUREMENTS AND RESULTS. $CO_2$ washout was analysed in a lung model by measuring single alveolar $CO_2$ concentration during DLT ventilation as compared to standard ETT ventilation, at different minute ventilation (6-14 L/min) and different $CO_2$-output levels (180 mL/min, 240 mL/min, and 300 mL/min). At a $CO_2$ output level of 240 mL/min the $CO_2$ washout was also compared to tidal volume-adjusted continuous TGI and expiratory synchronised TGI. Precision of tracheal pressure monitoring and PEEPi formation during DLT ventilation was evaluated by comparing pressure in each limb above the tube to refereoce tracheal pressure, varying I:E ratios (1:2, 1:1, and 2:1), tidal volumes (300-700 mL), breathing frequencies (15-25), and compliance (20-50 mL/cm $H_2O$). DLT ventilation had the same efficacy in removing $CO_2$ as continuous and expiratory synchrooised TGI, reducing single alveolar $CO_2$ concentration by 9-21% compared to normal ventilation. Tracheal pressure could be measured through the DLT with high precision. There was only marginal formation of PEEPi at tidal volumes ≤600 mL, I:E ratio ≤1:1, and compliance ≤35 mL/cm $H_2O$. CONCLUSIONS. The double lumen tube is as effective as tracheal gas insufflatioo io reducing $CO_2$ tension. Tracheal pressure and formation of PEEPi can be monitored with high precision without interrupting ventilation.

**Bench Testing of Pressure Support Ventilation with Three Different Generations of Ventilators**—Richard JC, Carlucci A, Breton L, Langlais N, Jaber S, Maggiore S, et al. Intensive Care Med 2002 Aug;28(8):1049-1057.

OBJECTIVE. The new generations of intensive care ventilators tend to be more innovative aod sophisticated than previous ones, but little is knowo about their respective performance for delivering pressure support ventilation (PSV) and how they compare to previous generations. DESIGN. Active lung model bench test. APPARATUS. Twenty-two commercially available ventilators classified into three categories: new generation ventilators (after 1993, n=7), previous generation (before 1993, n=6), and recent piston or turbine-based ventilators (n=9). MEASUREMENTS AND RESULTS. During PSV, the unloading efficacy of the assistance depends on the ventilator's ability to meet inspiratory flow demand. Three levels of flow (0.1 L/s, 0.6 L/s, and 1.2 L/s) were used to simulate inspiratory demand and the net area of the inspiratory airway pressure-time trace was calculated over the first 0.3 s, 0.5 s, and 1 s ($Area_{0.3}$, $Area_{0.5}$, and $Area_{tot}$) with three levels of PSV (5 cm $H_2O$, 10 cm $H_2O$, and 15 cm $H_2O$). To assess the respective role of pressure support delivery and triggering function, triggering sensitivity was assessed independently by measuring the time delay ($TD_{tg}$) aod the pressure fall ($\Delta P_{aw,tg}$) with two levels of inspiratory drive. All the new generation ventilators exhibited significantly better results than most of the previous generation ventilators regarding $Area_{0.3}$ and $TD_{tg}$, indicating large improvements in terms of triggering and pressurisation. CONCLUSION. Regarding PSV aod trigger performance, the new generation ventilators — but also some piston and turbine-based ventilators — outperform most of previous generatioo ventilators.

**Nitric Oxide Contamination of Hospital Compressed Air Improves Gas Exchange in Patients with Acute Lung Injury**—Tan K, Gene F, Delgado E, Kellum JA, Pinsky MR. Intensive Care Med 2002 Aug;28(8):1064-1072.

OBJECTIVE. We tested the hypothesis that NO contamination of hospital compressed air also improves $P_{aO_2}$ in patients with acute lung injury (ALI) aod following lung transplant (LTx). DESIGN. Prospective clinical study. SETTING. Cardiothoracic intensive care unit. PATIENTS. Subjects following cardiac surgery (CABG, n=7); with ALI ( n=7), and following LTx ( n=5). INTERVENTIONS. Four sequential 15-min steps at a constant $F_{IO_2}$ were used: hospital compressed air-$O_2$ (H1), $N_2$-$O_2$ (A1), repeat compressed air-$O_2$ (H2), and repeat $N_2$-$O_2$ (A2). MEASUREMENTS AND RESULTS. NO levels were measured from the endotracheal tube. Cardiorespiratory values included $P_{aO_2}$ were measured at the end of each step. $F_{IO_2}$ was 0.46±0.05, 0.53±0.15, and 0.47±0.06 (mean±SD) for three groups, respectively. Inhaled NO levels during H1 varied among subjects (30-550 ppb, 27-300 ppb, and 5-220 ppb, respectively). Exhaled NO levels were not detected in 4/7 of CABG (0-300 ppb), 3/6 of ALI (0-140 ppb), and 3/5 of LTx (0-59 ppb) patients during H1, whereas during A1 all but one patient in ALI and three CABG patients had measurable exhaled NO levels ( p<0.05). Small but significant decreases in $P_{aO_2}$ occurred for all groups from H1 to A1 and H2 to A2 (132-99 torr and 128-120 torr, p <0.01, respectively). There was no

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**Xopenex is contraindicated in patients with a history of hypersensitivity to levalbuterol HCl or racemic albuterol.**

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**BRIEF SUMMARY**

**INDICATIONS AND USAGE:** Xopenex (levalbuterol HCl) Inhalation Solution is indicated for the treatment or prevention of bronchospasm in adults, adolescents and children 6 years of age and older with reversible obstructive airway disease.

**CONTRAINDICATIONS:** Xopenex (levalbuterol HCl) Inhalation Solution is contraindicated in patients with a history of hypersensitivity to levalbuterol HCl or racemic albuterol.

**WARNINGS:** 1. Paradoxical Bronchospasm: Like other inhaled beta-adrenergic agonists, Xopenex Inhalation Solution can produce paradoxical bronchospasm, which may be life threatening. If paradoxical bronchospasm occurs, Xopenex Inhalation Solution should be discontinued immediately and alternative therapy instituted. It should be recognized that paradoxical bronchospasm, when associated with inhaled formulations frequently occurs with the first use of a new canister or vial. 2. Deterioration of Asthma: Asthma may deteriorate acutely over a period of hours or chronically over several days or longer. If the patient needs more doses of Xopenex Inhalation Solution than usual, this may be a marker of destabilization of asthma and requires reevaluation of the patient and treatment regimen, giving special consideration to the possible need for anti-inflammatory treatment, e.g., corticosteroids. 3. Use of Anti-Inflammatory Agents: The use of beta-adrenergic agonist bronchodilators alone may not be adequate to control asthma in many patients. Early consideration should be given to adding anti-inflammatory agents (e.g., corticosteroids) to the therapeutic regimen. 4. Cardiovascular Effects: Xopenex Inhalation Solution, like all other beta-adrenergic agonists, can produce a clinically significant cardiovascular effect in some patients, as measured by pulse rate, blood pressure, and/or symptoms. Although such effects are uncommon after administration of Xopenex Inhalation Solution at recommended doses, if they occur, the drug may need to be discontinued. In addition, beta-agonists have been reported to produce ECG changes, such as flattening of the T wave, prolongation of the QT interval, and ST segment depression. The clinical significance of these findings is unknown. Therefore, Xopenex Inhalation Solution, like all sympathomimetic amines, should be used with caution in patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, and hypertension. 5. Do Not Exceed Recommended Dose: Fatalities have been reported in association with excessive use of inhaled sympathomimetic drugs in patients with asthma. The exact cause of death is unknown, but cardiac arrest following an unexpected development of a severe acute asthmatic crisis and subsequent hypoxia is suspected. 6. Immediate Hypersensitivity Reactions: Immediate hypersensitivity reactions may occur after administration of racemic albuterol, as demonstrated by rare cases of urticaria, angioedema, rash, bronchospasm, anaphylaxis, and oropharyngeal edema. The potential for hypersensitivity must be considered in the clinical evaluation of patients who experience immediate hypersensitivity reactions while receiving Xopenex Inhalation Solution.

**PRECAUTIONS: General:** Levalbuterol HCl, like all sympathomimetic amines, should be used with caution in patients with cardiovascular disorders, especially coronary insufficiency, hypertension, and cardiac arrhythmias, in patients with convulsive disorders, hyperthyroidism, or diabetes mellitus, and in patients who are unusually responsive to sympathomimetic amines. Clinically significant changes in systolic and diastolic blood pressure have been seen in individual patients and could be expected to occur in some patients after the use of any beta-adrenergic bronchodilator. Large doses of intravenous racemic albuterol have been reported to aggravate preexisting diabetes mellitus and ketoacidosis. As with other beta-adrenergic agonist medications, levalbuterol may produce significant hypokalemia in some patients, possibly through intracellular shunting, which has the potential to produce adverse cardiovascular effects. The decrease is usually transient, not requiring supplementation.

**Information for Patients:** The action of Xopenex (levalbuterol HCl) Inhalation Solution may last up to 8 hours. Xopenex Inhalation Solution should not be used more frequently than recommended. Do not increase the dose or frequency of dosing of Xopenex Inhalation Solution without consulting your physician. If you find that treatment with Xopenex Inhalation Solution becomes less effective for symptomatic relief, your symptoms become worse, and/or you need to use the product more frequently than usual, you should seek medical attention immediately. While you are taking Xopenex Inhalation Solution, other inhaled drugs and asthma medications should be taken only as directed by your physician. Common adverse effects include palpitations, chest pain, rapid heart rate, headache, dizziness, and tremor or nervousness. If you are pregnant or nursing, contact your physician about the use of Xopenex Inhalation Solution. Effective and safe use of Xopenex Inhalation Solution requires consideration of the following information in addition to that provided under Patient's Instructions for Use (see complete prescribing information). Xopenex Inhalation Solution single-use low-density polyethylene (LDPE) vials should be protected from light and excessive heat. Store in the protective foil pouch between 20°C and 25°C (68°F and 77°F). Do not use after the expiration date stamped on the container. Unused vials should be stored in the protective foil pouch. Once the foil pouch is opened, the vials should be used within two weeks. Vials removed from the pouch, if not used immediately, should be protected from light and used within one week. Discard any vial if the solution is not colorless.

The drug compatibility (physical and chemical), efficacy, and safety of Xopenex Inhalation Solution when mixed with other drugs in a nebulizer have not been established.

**Drug Interactions:** Other short-acting sympathomimetic aerosol bronchodilators or epinephrine should be used with caution with levalbuterol. If additional adrenergic drugs are to be administered by any route, they should be used with caution to avoid deleterious cardiovascular effects.

1. Beta-blockers: Beta-adrenergic receptor blocking agents not only block the pulmonary effect of beta-agonists such as Xopenex (levalbuterol HCl) Inhalation Solution, but may also produce severe bronchospasm in asthmatic patients. Therefore, patients with asthma should not normally be treated with beta-blockers. However, under certain circumstances, e.g., as prophylaxis after myocardial infarction, there may be no acceptable alternatives to the use of beta-adrenergic blocking agents in patients with asthma. In this setting, cardioselective beta-blockers could be considered, although they should be administered with caution.

2. Diuretics: The ECG changes and/or hypokalemia that may result from the administration of non-potassium sparing diuretics (such as loop or thiazide diuretics) can be acutely worsened by beta-agonists, especially when the recommended dose of the beta-agonist is exceeded. Although the clinical significance of these effects is not known, caution is advised in the coadministration of beta-agonists with non-potassium sparing diuretics.

3. Digoxin: Mean decreases of 16% and 22% in serum digoxin levels were demonstrated after single-dose intravenous and oral administration of racemic albuterol, respectively, to normal volunteers who had received digoxin for 10 days. The clinical significance of these findings for patients with obstructive airway disease who are receiving levalbuterol HCl and digoxin on a chronic basis is unclear. Nevertheless, it would be prudent to carefully evaluate the serum digoxin levels in patients who are currently receiving digoxin and Xopenex Inhalation Solution.

4. Monoamine Oxidase Inhibitors or Tricyclic Antidepressants: Xopenex Inhalation Solution should be administered with extreme caution to patients being treated with monoamine oxidase inhibitors or tricyclic antidepressants, or within 2 weeks of discontinuation of such agents, because the action of levalbuterol HCl on the vascular system may be potentiated.

**Carcinogenesis, Mutagenesis, and Impairment of Fertility:** No carcinogenesis or impairment of fertility studies have been carried out with levalbuterol HCl alone. However, racemic albuterol sulfate has been evaluated for its carcinogenic potential and ability to impair fertility. In a 2-year study in Sprague-Dawley rats, racemic albuterol sulfate caused a significant dose-related increase in the incidence of benign leiomyomas of the mesovarium at and above dietary doses of 2 mg/kg (approximately 2 times the maximum recommended daily inhalation dose of levalbuterol HCl for adults and children on a mg/m² basis). In another study, this effect was blocked by the coadministration of propranolol, a nonselective beta-adrenergic antagonist. In an 18-month study in CD-1 mice, racemic albuterol sulfate showed no evidence of tumorigenicity at dietary doses up to 500 mg/kg (approximately 260 times the maximum recommended daily inhalation dose of levalbuterol HCl for adults and children on a mg/m² basis). In a 22-month study in the Golden hamster, racemic albuterol sulfate showed no evidence of tumorigenicity at dietary doses up to 50 mg/kg (approximately 35 times the maximum recommended daily inhalation dose of levalbuterol HCl for adults and children on a mg/m² basis). Levalbuterol HCl was not mutagenic in the Ames test or the CHO/HPRT Mammalian Forward Gene Mutation Assay. Although levalbuterol HCl has not been tested for clastogenicity, racemic albuterol sulfate was not clastogenic in a human peripheral lymphocyte assay or in an AH1 strain mouse micronucleus assay. Reproduction studies in rats using racemic albuterol sulfate demonstrated no evidence of impaired fertility at oral doses up to 50 mg/kg (approximately 55 times the maximum recommended daily inhalation dose of levalbuterol HCl for adults on a mg/m² basis).

**Teratogenic Effects — Pregnancy Category C:** A reproduction study in New Zealand White rabbits demonstrated that levalbuterol HCl was not teratogenic when administered orally at doses up to 25 mg/kg (approximately 110 times the maximum recommended daily inhalation dose of levalbuterol HCl for adults on a mg/m² basis). However, racemic albuterol sulfate has been shown to be teratogenic in mice and rabbits. A study in CD-1 mice given racemic albuterol sulfate subcutaneously showed cleft palate formation in 5 of 111 (4.5%) fetuses at 0.25 mg/kg (less than the maximum recommended daily inhalation dose of levalbuterol HCl for adults on a mg/m² basis) and in 10 of 108 (9.3%) fetuses at 2.5 mg/kg (approximately equal to the maximum recommended daily inhalation dose of levalbuterol HCl for adults on a mg/m² basis). The drug did not induce cleft palate formation when administered subcutaneously at a dose of 0.025 mg/kg (less than the maximum recommended daily inhalation dose of levalbuterol HCl for adults on a mg/m² basis). Cleft palate also occurred in 22 of 72 (30.5%) fetuses from females treated subcutaneously with 2.5 mg/kg of isoproterenol (positive control). A reproduction study in Stride Dutch rabbits revealed cranioschisis in 7 of 19 (37%) fetuses when racemic albuterol sulfate was administered orally at a dose of 50 mg/kg (approximately 110 times the maximum recommended daily inhalation dose of levalbuterol HCl for adults on a mg/m² basis). A study in which pregnant rats were dosed with radiolabeled racemic albuterol sulfate demonstrated that drug-related material is transferred from the maternal circulation to the fetus. There are no adequate and well-controlled studies of Xopenex Inhalation Solution in pregnant women. Because animal reproduction studies are not always predictive of human response, Xopenex Inhalation Solution should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. During marketing experience of racemic albuterol, various congenital anomalies, including cleft palate and limb defects, have been rarely reported in the offspring of patients being treated with racemic albuterol. Some of the mothers were taking multiple medications during their pregnancies. No consistent pattern of defects can be discerned, and a relationship between racemic albuterol use and congenital anomalies has not been established.

**Use in Labor and Delivery:** Because of the potential for beta-adrenergic agonists to interfere with uterine contractility, the use of Xopenex Inhalation Solution for the treatment of bronchospasm during labor should be restricted to those patients in whom the benefits clearly outweigh the risk.

**Tocolysis:** Levalbuterol HCl has not been approved for the management of preterm labor. The benefit-risk ratio when levalbuterol HCl is administered for tocolysis has not been established. Serious adverse reactions, including maternal pulmonary edema, have been reported during or following treatment of premature labor with beta -agonists, including racemic albuterol.

**Nursing Mothers:** Plasma levels of levalbuterol after inhalation of therapeutic doses are very low in humans, but it is not known whether levalbuterol is excreted in human milk. Because of the potential for tumorigenicity shown for racemic albuterol in animal studies and the lack of experience with the use of Xopenex Inhalation Solution by nursing mothers, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother. Caution should be exercised when Xopenex Inhalation Solution is administered to a nursing woman.

**Pediatrics:** The safety and efficacy of Xopenex (levalbuterol HCl) Inhalation Solution have been established in pediatric patients 6 years of age and older in one adequate and well-controlled clinical trial. Use of Xopenex in children is also supported by evidence from adequate and well-controlled studies of Xopenex in adults, considering that the pathophysiology and the drug's exposure level and effects in pediatric and adult patients are substantially similar. Safety and effectiveness of Xopenex in pediatric patients below the age of 6 years have not been established.

**Geriatrics:** Data on the use of Xopenex in patients 65 years of age and older are very limited. A very small number of patients 65 years of age and older were treated with Xopenex Inhalation Solution in a 4-week clinical study (n=2 for 0.63 mg and n=3 for 1.25 mg). In these patients, bronchodilation was observed after the first dose on day 1 and after 4 weeks of treatment. There are insufficient data to determine if the safety and efficacy of Xopenex Inhalation Solution are different in patients < 65 years of age and patients 65 years of age and older. In general, patients 65 years of age and older should be started at a dose of 0.63 mg of Xopenex Inhalation Solution. If clinically warranted due to insufficient bronchodilator response, the dose of Xopenex Inhalation Solution may be increased in elderly patients as tolerated, in conjunction with frequent clinical and laboratory monitoring, to the maximum recommended daily dose.

**ADVERSE REACTIONS (Adults and Adolescents ≥12 years old):** Adverse events reported in > 2% of patients receiving Xopenex Inhalation Solution or racemic albuterol and more frequently than in patients receiving placebo in a 4-week, controlled clinical trial are listed in **Table 1**.

**Table 1: Adverse Events Reported in a 4-Week, Controlled Clinical Trial in Adults and Adolescents ≥ 12 years old**

| | Percent of Patients | | | |
|---|---|---|---|---|
| Body System<br>Preferred Term | Placebo<br>(n=75) | Xopenex 1.25 mg<br>(n=73) | Xopenex 0.63 mg<br>(n=72) | Racemic albuterol 2.5 mg<br>(n=74) |
| Body as a Whole | | | | |
| Allergic reaction | 1.3 | 0 | 0 | 2.7 |
| Flu syndrome | 0 | 1.4 | 4.2 | 2.7 |
| Accidental injury | 0 | 2.7 | 0 | 0 |
| Pain | 1.3 | 1.4 | 2.8 | 2.7 |
| Back pain | 0 | 0 | 0 | 2.7 |
| Cardiovascular System | | | | |
| Tachycardia | 0 | 2.7 | 2.8 | 2.7 |
| Migraine | 0 | 2.7 | 0 | 0 |
| Digestive System | | | | |
| Dyspepsia | 1.3 | 2.7 | 1.4 | 1.4 |
| Musculoskeletal System | | | | |
| Leg cramps | 1.3 | 2.7 | 0 | 1.4 |
| Central Nervous System | | | | |
| Dizziness | 1.3 | 2.7 | 1.4 | 0 |
| Hypertonia | 0 | 0 | 0 | 2.7 |
| Nervousness | 0 | 9.6 | 2.8 | 8.1 |
| Tremor | 0 | 6.8 | 0 | 2.7 |
| Anxiety | 0 | 2.7 | 0 | 0 |
| Respiratory System | | | | |
| Cough increased | 2.7 | 4.1 | 1.4 | 2.7 |
| Infection viral | 9.3 | 12.3 | 6.9 | 12.2 |
| Rhinitis | 2.7 | 2.7 | 11.1 | 6.8 |
| Sinusitis | 2.7 | 1.4 | 4.2 | 2.7 |
| Turbinate edema | 0 | 1.4 | 2.8 | 0 |

The incidence of certain systemic beta-adrenergic adverse effects (e.g., tremor, nervousness) was slightly less in the Xopenex 0.63 mg group as compared to the other active treatment groups. The clinical significance of these small differences is unknown. Changes in heart rate 15 minutes after drug administration and in plasma glucose and potassium one hour after drug administration on day 1 and day 29 were clinically comparable in the Xopenex 1.25 mg and the racemic albuterol 2.5 mg groups (see **Table 2**). Changes in heart rate and plasma glucose were slightly less in the Xopenex 0.63 mg group compared to the other active treatment groups (see **Table 2**). The clinical significance of these small differences is unknown. After 4 weeks, effects on heart rate, plasma glucose, and plasma potassium were generally diminished compared with day 1 in all active treatment groups.

**Table 2: Mean Changes from Baseline in Heart Rate at 15 Minutes and in Glucose and Potassium at 1 Hour after First Dose (Day 1) in Adults and Adolescents ≥12 years old**

| | Mean Changes (day 1) | | |
|---|---|---|---|
| Treatment | Heart Rate (bpm) | Glucose (mg/dL) | Potassium (mEq/L) |
| Xopenex 0.63 mg, n=72 | 2.4 | 4.6 | −0.2 |
| Xopenex 1.25 mg, n=73 | 6.9 | 10.3 | −0.3 |
| Racemic albuterol 2.5 mg, n=74 | 5.7 | 8.2 | −0.3 |
| Placebo, n=75 | −2.8 | −0.2 | −0.2 |

No other clinically relevant laboratory abnormalities related to administration of Xopenex Inhalation Solution were observed in this study. In the clinical trials a slightly greater number of serious adverse events, discontinuations due to adverse events, and clinically significant ECG changes were reported in patients who received Xopenex 1.25 mg compared to the other active treatment groups. The following adverse events, considered potentially related to Xopenex, occurred in less than 2% of the 292 subjects who received Xopenex and more frequently than in patients who received placebo in any clinical trial:

| | |
|---|---|
| Body as a Whole | chills, pain, chest pain |
| Cardiovascular System | ECG abnormal, ECG change, hypertension, hypotension, syncope |
| Digestive System | diarrhea, dry mouth, dry throat, dyspepsia, gastroenteritis, nausea |
| Hemic and Lymphatic System | lymphadenopathy |
| Musculoskeletal System | leg cramps, myalgia |
| Nervous System | anxiety, hypesthesia of the hand, insomnia, paresthesia, tremor |
| Special Senses | eye itch |

The following events, considered potentially related to Xopenex, occurred in less than 2% of the treated subjects but at a frequency less than in patients who received placebo: asthma exacerbation, cough increased, wheezing, sweating, and vomiting.

**ADVERSE REACTIONS (Children 6 - 11 years old):** Adverse events reported in ≥ 2% of patients in any treatment group and more frequently than in patients receiving placebo in a 3-week, controlled clinical trial are listed in **Table 3**.

**Table 3: Most Frequently Reported Adverse Events (≥ 2% in Any Treatment Group) and More Frequently Than Placebo During the Double-Blind Period (ITT Population, 6 - 11 Years Old)**

| | Percent of Patients | | | | |
|---|---|---|---|---|---|
| Body System<br>Preferred Term | Placebo<br>(n=59) | Xopenex 0.31 mg<br>(n=66) | Xopenex 0.63 mg<br>(n=67) | Racemic albuterol 1.25 mg<br>(n=64) | Racemic albuterol 2.5 mg<br>(n=60) |
| Body as a Whole | | | | | |
| Abdominal pain | 3.4 | 0 | 1.5 | 3.1 | 6.7 |
| Accidental injury | 3.4 | 6.1 | 4.5 | 3.1 | 5.0 |
| Asthenia | 0 | 3.0 | 3.0 | 1.6 | 1.7 |
| Fever | 5.1 | 9.1 | 3.0 | 1.6 | 6.7 |
| Headache | 8.5 | 7.6 | 11.9 | 9.4 | 3.3 |
| Pain | 3.4 | 3.0 | 1.5 | 4.7 | 6.7 |
| Viral Infection | 5.1 | 7.6 | 9.0 | 4.7 | 8.3 |
| Digestive System | | | | | |
| Diarrhea | 0 | 1.5 | 6.0 | 1.6 | 0 |
| Hemic and Lymphatic | | | | | |
| Lymphadenopathy | 0 | 3.0 | 0 | 1.6 | 0 |
| Musculoskeletal System | | | | | |
| Myalgia | 0 | 0 | 1.5 | 1.6 | 3.3 |
| Respiratory System | | | | | |
| Asthma | 5.1 | 9.1 | 9.0 | 6.3 | 10.0 |
| Pharyngitis | 6.8 | 3.0 | 10.4 | 0 | 6.7 |
| Rhinitis | 1.7 | 6.1 | 10.4 | 3.1 | 5.0 |
| Skin and Appendages | | | | | |
| Eczema | 0 | 0 | 0 | 0 | 3.3 |
| Rash | 0 | 0 | 7.5 | 1.6 | 0 |
| Urticaria | 0 | 0 | 3.0 | 0 | 0 |
| Special Senses | | | | | |
| Otitis Media | 1.7 | 0 | 0 | 0 | 3.3 |

Note: Subjects may have more than one adverse event per body system and preferred term. Changes in heart rate, plasma glucose, and serum potassium are shown in **Table 4**. The clinical significance of these small differences is unknown.

**Table 4: Mean Changes from Baseline in Heart Rate at 30 Minutes and in Glucose and Potassium at 1 Hour after First Dose (Day 1) and Last Dose (Day 21) in Children 6-11 years old**

| | Mean Changes (Day 1) | | |
|---|---|---|---|
| Treatment | Heart Rate (bpm) | Glucose (mg/dL) | Potassium (mEq/L) |
| Xopenex 0.31 mg, n=66 | 0.8 | 4.9 | −0.31 |
| Xopenex 0.63 mg, n=67 | 6.7 | 5.2 | −0.36 |
| Racemic albuterol 1.25 mg, n=64 | 6.4 | 8.0 | −0.27 |
| Racemic albuterol 2.5 mg, n=60 | 10.9 | 10.8 | −0.56 |
| Placebo, n=59 | −1.8 | 0.6 | −0.05 |
| | Mean Changes (Day 21) | | |
| Treatment | Heart Rate (bpm) | Glucose (mg/dL) | Potassium (mEq/L) |
| Xopenex 0.31 mg, n=60 | 0 | 2.6 | −0.32 |
| Xopenex 0.63 mg, n=66 | 3.8 | 5.8 | −0.34 |
| Racemic albuterol 1.25 mg, n=62 | 5.8 | 1.7 | −0.18 |
| Racemic albuterol 2.5 mg, n=54 | 5.7 | 11.8 | −0.26 |
| Placebo, n=55 | −1.7 | 1.1 | −0.04 |

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correlation between inhaled NO during H1 and exhaled NO during A1 or the change in $P_{aO_2}$ from H1 to A1. CONCLUSIONS. Low-level NO contamination improves $P_{aO_2}$ in patients with ALI and following LTx.

**High Values of the Pulmonary Artery Wedge Pressure in Patients with Acute Lung Injury and Acute Respiratory Distress Syndrome**—Ferguson ND, Meade MO, Hallett DC, Stewart TE. Intensive Care Med 2002 Aug;28(8):1073-1077.

OBJECTIVE. To determine the incidence and severity of pulmonary artery wedge pressure (PAWP) elevation in patients with ALI/ARDS. In addition, to examine the effects of clinical variables on the presence of a high PAWP (>18 mm Hg) and the effect of an elevated PAWP on mortality. DESIGN AND PATIENTS. Post hoc analysis of 120 patients with or at high risk of ARDS, enrolled in a randomized controlled trial of pressure- and volume-limited ventilation. Patients with or at high risk of congestive heart failure were excluded from the original study. SETTING. Eight tertiary intensive care units. MEASUREMENTS AND RESULTS. Pulmonary artery catheters were inserted at the discretion of the attending physician, and PAWP was collected every 8 h when present. Of 120 subjects 71 (59%) had a pulmonary artery catheter (44 at randomization, 27 later). The mean maximum PAWP reading among patients was 22.5 mm Hg (95% CI 21.2-23.8) and mean median was 16.6 mm Hg (95% CI 15.6-17.5). Patients who met standard criteria for ARDS were more likely to develop a high PAWP. In a multivariate stepwise logistic regression model a persistently elevated PAWP (median >18 mm Hg) was a strong predictor of mortality after correction for baseline differences (OR estimate 6.82; 95% CI 1.66-37.81). CONCLUSIONS. We conclude that in this group of patients a PAWP higher than 18 mm Hg is common. Mandating a PAWP of 18 mm Hg or less may negatively impact clinical trials in which ARDS is an inclusion/exclusion criteria or an endpoint.

**Influence of Respiratory Rate on Gas Trapping During Low Volume Ventilation of Patients with Acute Lung Injury**—Richard JC, Brochard L, Breton L, Aboab J, Vandelet P, Tamion F, et al. Intensive Care Med 2002 Aug;28(8):1078-1083.

OBJECTIVE. Reduction in tidal volume ($V_t$) associated with increase in respiratory rate to limit hypercapnia is now proposed in patients with acute lung injury (ALI). The aim of this study was to test whether a high respiratory rate induces significant intrinsic positive end-expiratory pressure (PEEPi) in these patients. DESIGN. Prospective crossover study. SETTING. A medical intensive care unit. INTERVENTIONS AND MEASUREMENTS. Ten consecutive patients fulfilling criteria

for severe ALI were ventilated with a 6 mL/kg $V_t$, a total PEEP level at 13±3 cm $H_2O$ and a plateau pressure kept at 23±4 cm $H_2O$. The respiratory rate was randomly set below 20 breaths/min (17±3 breaths/min) and increased to 30 breaths/min (30±3 breaths/min) to compensate for hypercapnia. External PEEP was adjusted to keep the total PEEP and the plateau pressure constant. PEEPi was computed as the difference between total PEEP and external PEEP. The lung volume retained by PEEPi was then measured. RESULTS. Increase in respiratory rate resulted in significantly higher PEEPi (1.3±0.4 versus 3.9±1.1 cm $H_2O$, $p<0.01$) and trapped volume (70±43 versus 244±127 mL, $p<0.01$). External PEEP needed to be reduced from 11.9±3.4 to 9.7±2.9 cm $H_2O$ ($p<0.01$). $P_{aO_2}$ was not affected but the alveolar-arterial oxygen tension difference slightly worsened with the high respiratory rate ($p<0.05$). CONCLUSIONS. An increase in respiratory rate used to avoid $V_t$ reduction-induced hypercapnia may induce substantial gas trapping and PEEPi in patients with ALI.

**Influence of Inspiration:Expiration Ratio on Intracranial and Cerebral Perfusion Pressure in Acute Stroke Patients**—Georgiadis D, Schwarz S, Kollmar R, Baumgartner RW, Schwab S. Intensive Care Med 2002 Aug;28(8):1089-1093.

OBJECTIVE. We undertook this study to evaluate the influence of the inspiration:expiration (I:E) ratio on intracranial pressure and cerebral perfusion in patients with acute stroke. DESIGN. Ventilated patients with acute stroke were examined under a protocol involving variations of I:E ratio from 1:2 to 1:1 to 1:2 under positive end-expiratory pressure (PEEP) of 5.3 and - subsequently - 10.6 cm $H_2O$. Intracranial pressure was monitored with parenchymal or ventricular catheters. Mean arterial blood pressure, intracranial pressure (ICP), heart rate and peak mean flow velocity of the middle cerebral arteries were continuously recorded. SETTING. Neurological intensive care unit. PATIENTS. A total of 45 monitoring sessions were performed in 16 patients (subarachnoid haemorrhage 3, ischemic stroke 13). RESULTS. No significant changes in any of the parameters monitored were evident in association with the I:E ratio variations under either of the PEEP levels applied. It must be noted, though, that ICP exceeded 15 mm Hg in only 5/45 monitoring sessions, and never exceeded 20 mm Hg. CONCLUSIONS. Our preliminary results suggest that variations of the I:E ratio cause no significant changes in intracranial or cerebral perfusion pressure and, thus, can be safely used in patients with acute stroke without intracranial hypertension. The influence of I:E ratio variations on stroke patients with intracranial hypertension remains to be evaluated.

**Oxygenation Index, an Indicator of Optimal Distending Pressure During High-Frequency Oscillatory Ventilation?**—Van Genderingen HR, Van Vught JA, Jansen JR, Duval EL, Markhorst DG, Versprille A. Intensive Care Med 2002 Aug;28(8):1151-1156.

OBJECTIVE. To test the hypothesis that, during high-frequency oscillatory ventilation (HFOV) of pigs with acute lung injury, the oxygenation index (OI = Paw× $F_{IO_2}$×100/ $P_{aO_2}$) is minimal at the lowest continuous distending pressure ($P_{aw}$), where the physiological shunt fraction is below 0.1 ($P_{aw,optimal}$). DESIGN AND SETTING. Prospective, observational study in a university research laboratory. SUBJECTS. Eight Yorkshire pigs weighing 12.0 ±0.5 kg, with lung injury induced by lung lavage. INTERVENTIONS. After initiation of HFOV, the pigs were subjected to a stepwise increase of $P_{aw}$ to obtain under-inflation, optimal inflation and over-distension of the lungs (inflation) in series, followed by a similar decrease of $P_{aw}$ (deflation). MEASUREMENTS AND RESULTS. At each $P_{aw}$ level, the OI and physiological shunt fraction were determined. The OI reached a minimum of 6.2 ±1.4 at $P_{aw}$ 30 ±4 cm $H_2O$ during inflation and a minimum of 2.4 ±0.3 at Paw 13 ±2 cm H2O during deflation. $P_{aw,optimal}$ was 32 ±6 cm$H_2O$ on the inflation limb and 14 ±2 cm $H_2O$ on the deflation limb. The difference between the $P_{aw}$ at minimal OI and $P_{aw,optimal}$ was -1.9 ± 4.2 cm $H_2O$ (NS) during inflation and -1.5 ± 1.6 cm $H_2O$ ( $p<0.05$) during deflation. In 15 out of the 16 comparisons, the difference in $P_{aw}$ was within one step (± 3 cm $H_2O$). CONCLUSION. The minimal OI is indicative for the $P_{aw}$ where oxygenation is optimal during HFOV in surfactant-depleted pigs.

**More Reliable Oximetry Reduces the Frequency of Arterial Blood Gas Analyses and Hastens Oxygen Weaning After Cardiac Surgery: A Prospective, Randomized Trial of the Clinical Impact of a New Technology**—Durbin CG Jr, Rostow SK. Crit Care Med 2002 Aug;30(8):1735-1740.

OBJECTIVE: Evaluation of the impact on clinical care of improved, innovative oximetry technology. DESIGN: Randomized, prospective trial. SETTING: Postcardiac surgery intensive care unit in a major teaching hospital. PATIENTS: A total of 86 patients after undergoing coronary artery bypass surgery. INTERVENTIONS: All patients were monitored with two oximeters, one employing conventional oximetry (conventional pulse oximeter, CPO) and one using an improved innovative technology (innovative pulse oximeter, IPO), on different fingers of the same hand. The outputs from both devices were collected continuously by computer, but only one device was randomly selected and displayed for clinicians. MEASUREMENTS AND MAIN RESULTS: The amount and percentage of nonfunctional monitoring time was collected and found to be much greater for the CPO than the IPO (8.7% ± 16.4% for CPO vs. 1.2% ± 3.3% for IPO, p =0.000256). Time to extubation was not different between the two groups (634 ± 328 mins for IPO vs. 706 ± 459 mins for CPO). Clinicians managing patients with the more reliable IPO weaned patients faster to an $F_{IO_2}$ of 0.40 (176 ± 111 mins for IPO vs. 348 ± 425 mins for CPO, p =0.0125), obtained fewer arterial blood gas measurements (2.7 ± 1.2 for IPO vs. 4.1 ± 1.6 for CPO, p =0.000015), and made the same number of ventilator changes during this weaning process (2.9 ± 1.2 for IPO vs. 2.9 ± 1.7 for CPO). CONCLUSIONS: Provision of more reliable oximetry allows caregivers to act in a more efficient and cost-effective manner in regard to oxygen weaning and use of arterial blood gas measurements. Investigating the effect of a monitor on the process of care, rather than simply its accuracy and precision, is a useful, relevant paradigm for evaluating the value and impact of a new technology.

**Air Cysts and Bronchiectasis Prevail in Nondependent Areas in Severe Acute Respiratory Distress Syndrome: A Computed Tomographic Study of Ventilator-Associated Changes**—Treggiari MM, Romand JA, Martin JB, Suter PM. Crit Care Med 2002 Aug;30(8):1747-1752.

OBJECTIVE: To investigate prevalence and spatial distribution of air cysts and bronchiectasis associated with mechanical ventilation in patients with severe acute respiratory distress syndrome. DESIGN: Retrospective observational study. SETTING: University hospital intensive care division. SUBJECTS: A total of 21 patients with severe acute respiratory distress syndrome requiring prolonged mechanical ventilation and undergoing thoracic computed tomographic scanning. MEASUREMENTS AND MAIN RESULTS: Lung fields were anatomically divided according to functional bronchial divisions in ten segments on each side. Air cysts, bronchiectasis, and the percentage of normal and abnormal tissue were quantified for each segment and correlated to the duration and variables of mechanical ventilation. Air cysts prevailed in nondependent compared with dependent areas (38% ± 5% vs. 9% ± 3%, respectively; p <0.01). With mechanical ventilation longer than 10 days, the odds ratio was 13.1 (95% confidence interval, 1.4-118.7) for air cysts and for bronchiectasis 17.6 (95% confidence interval, 2.8-109.6). The amount of abnormal parenchyma correlated with duration of mechanical ventilation on high end-inspiratory pressure but not with tidal volume or minute ventilation. The presence of pneumothorax was not correlated with ventilation settings but with the amount of consolidated tissue revealed by the computed tomographic scan. CONCLUSIONS: These findings suggest

predominant ventilator-induced lung damage in better ventilated areas (i.e., nondependent regions). Severity of changes revealed by computed tomographic imaging seems to be associated mainly with the high inspiratory pressures required and the length of mechanical ventilation.

**Repeated Derecruitments Accentuate Lung Injury During Mechanical Ventilation**—Suh GY, Koh Y, Chung MP, An CH, Kim H, Jang WY, et al. Crit Care Med 2002 Aug;30(8):1848-1853.

OBJECTIVE: This study was performed to test the hypothesis that derecruitment itself might accentuate lung injury during mechanical ventilation. SETTING: Randomized, controlled trial. SETTING: Experimental laboratory. SUBJECTS: New Zealand White rabbits (2.8-3.5 kg). INTERVENTION: Twenty-four rabbits were ventilated in pressure-controlled mode with constant tidal volume (10 mL/kg). After lung injury was induced by repeated saline lavage ($P_{aO_2}$ <100 torr, 13.3 kPa), a pressure-volume curve was drawn to calculate the lower inflection point ($P_{flex}$), and randomization was done. The control group (n = 8) received ventilation with positive end-expiratory pressure (PEEP) fixed at $P_{flex}$ for 3 hrs. The nonderecruitment group (n = 8) was ventilated at PEEP of 2 mm Hg (2.7 cm $H_2O$) for the initial hour and then PEEP of $P_{flex}$ for the remaining 2 hrs. The derecruitment group (n = 8) was ventilated for 3 hrs with six 30-min cycles consisting of 10 mins at PEEP of 2 mm Hg (2.7 cm $H_2O$) and 20 mins at PEEP of $P_{flex}$ to induce repeated derecruitments. MEASUREMENTS AND MAIN RESULTS: Variables of gas exchange, mechanics, and hemodynamics were measured, and histologic evaluation was done. In the control group, $P_{aO_2}$ remained >500 torr (66.7 kPa) for 3 hrs. In the nonderecruitment group, $P_{aO_2}$ was 40 ± 16 (mean ± SD) torr (5.3 ± 2.1 kPa) at 1 hr but increased to >500 torr (66.7 kPa) for the remaining 2 hrs after increase in PEEP to $P_{flex}$. In the derecruitment group, there was progressive decline in $P_{aO_2}$ with each derecruitment to 220 ± 130 torr (29.3 ± 17.3 kPa) at 3 hrs ($p < 0.05$ compared with other groups). Histologically there was more hyaline membrane formation in the derecruitment group compared with control ($p < 0.05$) and significantly higher mean bronchiolar injury score in the derecruitment group (1.92 ± 0.78) than both control (0.50 ± 0.50) and nonderecruitment (0.78 ± 0.42) groups ($p < 0.05$). CONCLUSION: Repeated derecruitments can accentuate lung injury during mechanical ventilation.

**Local Warming and Insertion of Peripheral Venous Cannulas: Single Blinded Prospective Randomised Controlled Trial and Single Blinded Randomised Crossover Trial**—Lenhardt R, Seybold T, Kimberger O, Stoiser B, Sessler DI. BMJ 2002 Aug 24;325(7361):409.

OBJECTIVE: To determine whether local warming of the lower arm and hand facilitates peripheral venous cannulation. DESIGN: Single blinded prospective randomised controlled trial and single blinded randomised crossover trial. SETTING: Neurosurgical unit and haematology ward of university hospital. PARTICIPANTS: 100 neurosurgical patients and 40 patients with leukaemia who required chemotherapy. INTERVENTIONS: Neurosurgical patients' hands and forearms were covered for 15 minutes with a carbon fibre heating mitt. Patients were assigned randomly to active warming at 52 degrees C or passive insulation (heater not activated). The same warming system was used for 10 minutes in patients with leukaemia. They were assigned randomly to active warming or passive insulation on day 1 and given alternative treatment during the subsequent visit. MAIN OUTCOME MEASURES: PRIMARY: success rate for insertion of 18 gauge cannula into vein on back of hand. SECONDARY: time required for successful cannulation. RESULTS: In neurosurgical patients, it took 36 seconds (95% confidence interval 31 to 40 seconds) to insert a cannula in the active warming group and 62 (50 to 74) seconds in the passive insulation group (p=0.002). Three (6%) first attempts failed in the active warming group compared with 14 (28%) in the passive insulation group (p=0.008). The crossover study in patients with leukaemia showed that insertion time was reduced by 20 seconds (8

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to 32, p=0.013) with active warming and that failure rates at first attempt were 6% with warming and 30% with passive insulation (p<0.001). CONCLUSIONS: Local warming facilitates the insertion of peripheral venous cannulas, reducing both time and number of attempts required. This may decrease the time staff spend inserting cannulas, reduce supply costs, and improve patient satisfaction.

**Involuntary Smoking and Asthma Severity in Children: Data from the Third National Health and Nutrition Examination Survey**—Mannino DM, Homa DM, Redd SC. Chest 2002 Aug;122(2):409-415.

STUDY OBJECTIVES: We sought to determine the indicators of asthma severity among children in the United States with high and low levels of tobacco smoke exposure. DESIGN: Cross-sectional study. SETTING: Nationally representative survey of participants in the Third National Health and Nutrition Examination Survey (from 1988 to 1994). PARTICIPANTS: Five hundred twenty-three children with physician-diagnosed asthma. MEASUREMENTS AND RESULTS: We stratified the study participants into tertiles on the basis of serum levels of cotinine (a metabolite of nicotine that indicates tobacco smoke exposure). We used logistic and linear regression modeling, adjusting for known covariates, to determine the effect of high environmental tobacco smoke exposure on the following outcomes: asthma severity (determined using reported symptom and respiratory illness frequency); lung function; physician visits; and school absence. Among our study sample, 78.6% of children had mild asthma, 6.8% of children had moderate asthma, and 14.6% of children had severe asthma. Asthmatic children with high levels of smoke exposure, compared with those with low levels of exposure, were more likely to have moderate or severe asthma (odds ratio, 2.7 95% confidence interval [CI], 1.1 to 6.8) and decreased lung function, with a mean $FEV_1$ decrement of 213 mL or 8.1% (95% CI, -14.7 to -3.5). CONCLUSIONS: Involuntary smoke exposure is associated with increased asthma severity and worsened lung function in a nationally representative group of US children with asthma.

**Using Quality of Life to Predict Hospitalization and Mortality in Patients with Obstructive Lung Diseases**—Fan VS, Curtis JR, Tu SP, McDonell MB, Fihn SD; Ambulatory Care Quality Improvement Project Investigators. Chest 2002 Aug;122(2):429-436.

STUDY OBJECTIVES: Condition-specific measures of quality of life (QOL) for patients with COPD have been demonstrated to be highly reliable and valid, but they have not conclusively been shown to predict hospitalization or death. OBJECTIVE: We sought to determine whether a brief, self-administered, COPD-specific QOL measure, the Seattle Obstructive Lung Disease Questionnaire (SOLDQ), could accurately predict hospitalizations and death. DESIGN: Prospective cohort study. SETTING: Patients enrolled in the primary care clinics at seven Department of Veterans Affairs (VA) medical centers participating in the Ambulatory Care Quality Improvement Project. PATIENTS: Of 24,458 patients who completed a health inventory, 5,503 reported having chronic lung disease. The 3,282 patients who completed the baseline SOLDQ were followed for 12 months. MEASUREMENTS: Hospitalization and all-cause mortality during the 1-year follow-up period. RESULTS: During the follow-up period, 601 patients (18.3%) were hospitalized, 141 (4.3%) for COPD exacerbations, and 167 patients (5.1%) died. After adjusting for age, VA hospital site, distance to the VA hospital, employment status, and smoking status, the relative risk of any hospitalization among patients with scores on the emotional, physical, and coping skills scales of the SOLDQ that were in the lowest quartile, when compared to the highest quartile, were 2.0 (95% confidence interval [CI], 1.5 to 2.6), 2.5 (95% CI, 1.9 to 3.4), and 1.9 (95% CI, 1.5 to 2.5), respectively. When hospitalizations were restricted to those specifically for COPD, the odds ratio (OR) for the lowest quartile of physical function was 6.0 (95% CI, 3.1 to 11.5). Similarly, patients in the lowest quartile of physical function also had an increased risk of death (OR, 6.8; 95% CI, 3.3 to 13.8). When adjusted for comorbidity (OR, 0.8; 95% CI, 0.5 to 1.2), long-term steroid use (OR, 2.8; 95% CI, 1.6 to 4.9), and prior hospitalization for COPD (OR, 4.5; 95% CI, 2.2 to 9.2), patients having baseline SOLDQ physical function scores in the lowest quartile had an odds of hospitalization for COPD that was fivefold higher than patients with scores in the highest quartile (OR, 5.0; 95% CI, 2.6 to 9.7). CONCLUSIONS: Lower QOL is a powerful predictor of hospitalization and all-cause mortality. Brief, self-administered instruments such as the SOLDQ may provide an opportunity to identify patients who could benefit from preventive interventions.

**Refillable Oxygen Cylinders May Be an Alternative for Ambulatory Oxygen Therapy in COPD**—Cuvelier A, Muir JF, Chakroun N, Aboab J, Onea G, Benhamou D. Chest 2002 Aug;122(2):451-456.

STUDY OBJECTIVES: To compare, in clinical conditions, the efficacy of refilled oxygen cylinders ($O_2$-HFs) in improving oxygenation and exercise capacity of patients with COPD during a 6-min walking test. DESIGN: Prospective randomized study with a cross-over design. SETTING: A university teaching hospital. PATIENTS: Ten patients with COPD, in a stable state and previously treated with long-term domiciliary oxygen therapy. Baseline characteristics were as follows: age, 65 ± 7 years; $P_{aO_2}$ on room air, 55.4 ± 6.3 mm Hg; $P_{aCO_2}$ on room air, 46.2 ± 7.4 mm Hg; $FEV_1$/vital capacity, 47 ± 7%; and $FEV_1$, 30 ± 7% of predicted value (mean ± SD). DESIGN: All patients performed three successive 6-min walking tests, the first test in room air and the other tests in a randomized order with either a conventional oxygen cylinder ($O_2$-C) or an $O_2$-HF. MEASUREMENTS AND RESULTS: The fraction of inspired oxygen ($F_{IO_2}$) delivered by $O_2$-HFs was significantly lower than the $F_{IO_2}$ delivered by $O_2$-Cs (94.2 ± 2.6% vs 98.8 ± 4.9%, p = 0.02). Mean $O_2$-HF and $O_2$-C weights before the walking tests were similar (3,510 ± 251 g and 3,770 ± 142 g, respectively; p = 0.09). Mean transcutaneous oxygen saturation was similarly improved with both oxygen delivery systems. Mean distances with $O_2$-C (373.5 ± 81 m) and $O_2$-HF (375 ± 97 m) were not different but significantly improved, as compared with room air (334.5 ± 90 m; p = 0.03 and 0.02, respectively). Dyspnea sensations were similar for the three tests. CONCLUSION: $O_2$-HFs are as efficient as $O_2$-Cs for performing short-term exercises. Because of a lower cost, pressurizing units may be worthwhile for improving ambulatory oxygen therapy and pulmonary rehabilitation programs.

**Effects of Training with Heliox and Noninvasive Positive Pressure Ventilation on Exercise Ability in Patients with Severe COPD**—Johnson JE, Gavin DJ, Adams-Dramiga S. Chest 2002 Aug;122(2):464-472.

STUDY OBJECTIVES: We sought to determine whether breathing heliox or using nasal noninvasive positive pressure ventilation (NIPPV) would produce immediate improvements in exercise capability in patients with COPD, and whether training for 6 weeks with one of these modalities would result in greater exercise improvement than with training unassisted. SETTING: US military medical center. METHODS: Thirty-nine patients with severe COPD (mean $FEV_1$ of 33.5% predicted) underwent three incremental treadmill tests to exhaustion unassisted, breathing heliox, or breathing with NIPPV. They were then randomized to undergo 6 weeks of twice-weekly rehabilitation with unassisted exercise training (UT group), training while breathing heliox (HT group), or training while breathing with NIPPV (NT group). The three exercise tests were then repeated. RESULTS: Heliox treatment did not produce any immediate benefit in exercise time or maximum workload in the 39 patients initially tested, the 32 patients who completed the protocol, or the HT group. Furthermore, no training advantage was evident in the HT group (n = 10) compared to the UT group (n = 11). NIPPV did not produce an immediate benefit in the initial tests.

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but produced a small increase in exercise time in the 32 patients completing the protocol in the final tests. This effect was primarily because of the NT group, who exercised significantly longer (mean ± SD, 16.8 ± 4.9 min vs 14.2 ± 5.6 min, p = 0.0045) and to a higher workload (4.46 ± 1.55 metabolic equivalents [METs] vs 4.09 ± 1.75 METs, respectively; p = 0.038) when tested using the ventilator. Compared to the UT group, the NT group started out with a lower exercise time (7.9 ± 3.5 min vs 12.3 ± 5.2 min, p = 0.031) in preliminary testing, but the statistical difference was eliminated in the final tests (14.2 ± 5.6 min vs 16.0 ± 5.8 min, respectively; p = 0.451). The NT group actually slightly exceeded the UT group when they used the ventilator in final testing, although this was not statistically significant (16.8 ± 4.9 min vs 16.0 ± 5.8 min, respectively). CONCLUSION: Heliox treatment does not appear to offer an immediate or training advantage with exercise in patients with COPD. For patients who have undergone regular exercise conditioning with NIPPV, use of the ventilator produces an immediate improvement in both exercise time and maximum workload attained, and it may confer a training advantage.

**Teaching Time for Metered-Dose Inhalers in the Emergency Setting**—Numata Y, Bourbeau J, Ernst P, Duquette G, Schwartzman K. Chest 2002 Aug;122(2):498-504.

OBJECTIVES: In some acute-care settings, practitioners are reluctant to institute bronchodilator therapy with metered-dose inhalers (MDIs) as standard management. Such therapy requires that personnel ensure optimal use of these devices. We prospectively evaluated the time required to teach patients correct inhaler use for the emergency treatment of asthma and COPD, and patient factors associated with duration of teaching. DESIGN: MDI arm within a single-center randomized clinical trial comparing bronchodilator administration by MDI with a delivery enhancement device (MDI/DED) vs delivery by wet nebulizer. SETTING: All subjects were treated for asthma or COPD exacerbations at the respiratory acute-care day hospital of the Montreal Chest Institute, immediately after presentation to our emergency department. Inhaler-use education was provided according to a predetermined protocol. MEASUREMENTS: Subjects' baseline characteristics were obtained from medical charts, spirometry, and questionnaires; satisfaction was evaluated by questionnaire. All inhaler-use education was observed and timed. RESULTS: Sixty-one patients with asthma (median age, 46 years) and 32 patients with COPD (median age, 68.5 years) were randomized to treatment by MDI/DED. Mean $FEV_1$ (percent predicted) was 63.5% for patients with asthma and 39.5% for patients with COPD. Five patients could not complete MDI teaching and therefore received subsequent treatment by wet nebulization. For the 88 other patients, the median teaching time was 6.5 min. Shorter teaching-time requirements were independently associated with higher initial arterial oxygen saturation, home DED use after previous MDI instruction, and a single initial bronchodilator treatment by wet nebulization. Most subjects expressed satisfaction with MDI/DED teaching and treatment. CONCLUSIONS: Successful MDI/DED teaching followed by self-medication is feasible in the emergency setting, based on a simple protocol. A single bronchodilator dose administered by wet nebulization may facilitate subsequent MDI teaching.

**An Individually Adjustable Oral Appliance vs Continuous Positive Airway Pressure in Mild-to-Moderate Obstructive Sleep Apnea Syndrome**—Randerath WJ, Heise M, Hinz R, Ruehle KH. Chest 2002 Aug;122(2):569-575.

BACKGROUND: For the treatment of nonsevere obstructive sleep apnea syndrome (OSAS), mandibular advancement devices (MADs) are

employed as an alternative to nasal continuous positive airway pressure (CPAP) therapy. However, very few specific data on the effectiveness of MADs in this group of patients are available. We therefore compared an individually adjustable intraoral sleep apnea device (ISAD) that permits movements of the lower jaw in three dimensions, with CPAP in the treatment of patients with an apnea/hypopnea index (AHI) ≤ 30/h. METHODS: In a randomized crossover study, 16 men and 4 women (mean ± SD age, 56.5 ± 10.2 years; body mass index, 31.2 ± 6.4; AHI, 17.5 ± 7.7/h) were treated for 6 weeks with each modality. RESULTS: In the initial phase, a significant improvement in AHI (baseline, 17.5 ± 7.7/h; ISAD, 10.5 ± 7.5/h [$p < 0.05$]; CPAP, 3.5 ± 2.9/h [$p < 0.01$]) and in breathing-related arousals (baseline, 8.9 ± 6.1/h; ISAD, 3.7 ± 3.3/h [$p < 0.01$]; CPAP, 1.4 ± 1.6/h [$p < 0.01$]) was achieved with both modalities. Considering all 20 subjects, after 6 weeks of treatment, normalization of the respiratory parameters was seen only with CPAP. However, 30% of the patients had a lasting reduction in AHI to < 10/h with the ISAD also. The patients considered the ISAD to be easier to use (scale of 1 to 6: ISAD, 1.8 ± 1.1; CPAP, 3.1 ± 1.5 [$p < 0.05$]), and indicated greater utilization of the device in comparison with CPAP. CONCLUSION: Even in patients with mild-to-moderate OSAS, CPAP is the more effective long-term treatment modality. In the individual case, the better compliance seen with the ISAD may be advantageous.

**Paradoxical Movement of the Lateral Rib Margin (Hoover Sign) for Detecting Obstructive Airway Disease**—Garcia-Pachon E. Chest 2002 Aug;122(2):651-655.

STUDY OBJECTIVE: To evaluate the diagnostic accuracy of Hoover sign for detecting obstructive airway disease (OAD), compared with wheezes, rhonchi, reduced breath sounds, and clinical impression, and to analyze the observer agreement on these signs. DESIGN: Prospective, blind comparison, with a reference standard (spirometry) among a consecutive series of patients. SETTING: Outpatient pulmonary clinic. PATIENTS: One hundred seventy-two patients (117 men [68%] and 55 women [32%]), who were > 40 years of age, had not been known previously by the participating physicians, and met at least one of the following criteria: smokers of > 20 pack-years; patients who had received a diagnosis of or had self-reported COPD (or chronic bronchitis or emphysema); patients who had received inhaler bronchodilator treatment for > 6 months; or patients with any degree of dyspnea. MEASUREMENTS: Patients were examined by a first-year resident in family medicine and by a pulmonologist. Spirometry was performed by a blinded trained technician. OAD was defined as an $FEV_1/FVC$ ratio of < 0.70. RESULTS: OAD was present in 64 patients (37%). Observer agreement (kappa statistic) was 0.74 for Hoover sign and was lower for the rest of the signs. Hoover sign had a sensitivity of 58% and a specificity of 86% for detecting OAD, and it had a positive likelihood ratio of 4.16, which was higher than that of the other signs. CONCLUSIONS: Hoover sign, a frequently forgotten sign, is easy to recognize and is useful for detecting OAD.

**Pneumothorax in the ICU: Patient Outcomes and Prognostic Factors**—Chen KY, Jerng JS, Liao WY, Ding LW, Kuo LC, Wang JY, Yang PC. Chest 2002 Aug;122(2):678-683.

STUDY OBJECTIVE: To identify the prognostic factors for pneumothorax in patients in the ICU. DESIGN: Retrospective cohort study. SETTING: ICU at a university-based teaching hospital. PATIENTS AND METHODS: Sixty patients developed pneumothoraces in the ICU during a period of 36 months. Medical records relating to patients' age, sex, underlying diseases, associated medical conditions, reasons for admission, acute physiology and chronic health evaluation (APACHE) II scores, procedures performed before the development of pneumothorax, occurrences of tension pneumothorax, duration of chest tube placement, chest tube removal, duration of ICU stay, and patient outcomes all were analyzed. A multivariate logistic regression model was applied with variables that were significantly associated with survival in the univariate analysis. The probabilities of chest tube removal were calculated using the Kaplan-Meier method. RESULTS: Thirty-five patients (58%) had procedure-related pneumothoraces. The procedure that most commonly caused pneumothoraces was thoracentesis (n = 19; 54%), followed by central vein/pulmonary artery catheterization (n = 14; 40%) and bronchoscopy/transbronchial lung biopsy (n = 8; 23%). A multivariate logistic regression analysis also showed that pneumothorax due to barotrauma ($p = 0.001$), tension pneumothorax ($p = 0.0023$), and concurrent septic shock ($p = 0.0476$) were significantly and independently associated with death. The log-rank test revealed that the success rate of chest tube removal was higher in patients with procedure-related pneumothoraces ($p = 0.0055$). CONCLUSIONS: Patients with procedure-related pneumothoraces had better outcomes. Patients with pneumothoraces occurring in the ICU due to barotrauma, or a complicating tension pneumothoraces, carry a higher risk of mortality.

**Organophosphate Intoxication As a Consequence of Mouth-to-Mouth Breathing from an Affected Case**—Koksal N, Buyukbese MA, Guven A, Cetinkaya A, Hasanoglu HC. Chest 2002 Aug;122(2):740-741.

We report three cases of organophosphate (OP) poisoning. One patient was a 19-year-old woman who drank OP compounds in an attempt at suicide. The other two patients became intoxicated on the way to the hospital during mouth-to-mouth breathing. The first patient died in the emergency department, and the other two were taken to the ICU. There, they were treated with atropine and pralidoxime. Three days later, all symptoms and signs had disappeared, and they were discharged from the hospital satisfactorily.

**Controlled Trial of Three Weeks Nicotine Replacement Treatment in Hospital Patients Also Given Advice and Support**—Hand S, Edwards S, Campbell IA, Cannings R. Thorax 2002 Aug;57(8):715-718.

BACKGROUND: Smoking is a major public health issue, estimated as causing 120 000 deaths in the UK per year. Smoking cessation is an important aspect of the treatment of many diseases. Nicotine replacement therapy (NRT) has been shown to increase cessation rates among healthy volunteers and in general practice, but it is not clear whether it has an effect in hospital patients. METHODS: Patients referred by their hospital doctor to the smoking cessation counsellor and who agreed to participate in the study were randomised to receive either NRT given as a nicotine patch daily and a nicotine inhalator on an as needed basis plus advice and support (AS+NRT), or to receive just advice and support (AS). Claims of smoking cessation were validated at 1 week, 3 months, 6 months, and 1 year by carbon monoxide (CO) breath testing. RESULTS: A total of 245 patients were randomised, 136 AS+NRT and 109 AS. There were no significant demographic differences between the two groups at baseline. At 1 year 35 (14%) had sustained cessation confirmed by a CO breath test, 20/136 (15%) AS+NRT and 15/109 (14%) AS, p=0.857. One hundred and ten patients gave up smoking for at least 1 week, 54% AS+NRT and 33% AS ($p<0.001$). By 6 months there was no significant difference between the two groups (22/136 (16%) AS+NRT and 15/109 (14%) AS). CONCLUSION: In hospital patients NRT, given as regular daily patches plus an inhalator to be used as needed, did not add to the smoking cessation rate achieved at 1 year by regular advice and support, despite significantly increasing the cessation rate at 1 week.

**Risk of Tuberculosis Among Healthcare Workers: Can Tuberculosis Be Considered As an Occupational Disease?**—Kiline O, Ucan ES, Cakan MD, Ellidokuz MD, Ozol MD, Sayiner A, Ozsoz MD. Respir Med 2002 Jul;96(7):506-510.

This study aimed to determine the incidence of tuberculosis among hospital employees in four major urban institutions, which employ nearly 90%

of all hospital workers caring for adult patients in a city of 2.5 million inhabitants. It also had the objective of finding out whether this incidence changes according to the in-hospital setting, i.e. the departments, and thus, whether tuberculosis can be considered to pose an occupational risk. The study population consisted of all healthcare workers of the four hospitals between 1986 and 1998. From these, those who developed tuberculosis within this period were determined and were considered as the case group. All the remaining employees constituted the control group. Fifty-nine healthcare workers were found to have developed the disease. The annual incidence was found to range between 0.016 and 0.139%. Tuberculosis was seen 3 times more frequently among the hospital employees than the general population. The workers in departments of chest diseases were found to have a higher risk than those of other departments (OR: 6.37, CI: 3.69-11.00). Similarly, the nurses were also at a higher risk than the doctors (OR: 2.63, CI: 1.12-6.36). These findings suggest that tuberculosis can be considered as an occupational disease.

**Evaluation of Long-Term Efficacy of an Asthma Education Programme in an Out-Patient Clinic**—Yilmaz A, Akkaya E. Respir Med 2002 Jul;96(7):519-524.

The aim of the present study was to evaluate long-term efficacy of a patient education programme in an asthma out-patient clinic. The study included two groups. Educational group consisted of 25 patients who were given special education for one year. Usual care group included 27 patients who were not given special education. All patients were evaluated after 3 years follow-up period. Mean per cent asthma knowledge score (KS%), mean per cent demonstration score (DS%), daytime and nighttime symptom scores, Aas score, and pulmonary function tests were measured. The asthma-quality-of-life assessment was performed. The rate of application to emergency room and admission to hospital for last 1 year had been calculated. KS% was higher in educational group than in usual care group ($p < 0.001$). Daytime score was $0.3 \pm 0.6$ in educational group and was $0.8 \pm 1.2$ in usual care group ($p = 0.08$). Nighttime symptom score was found to be $0.5 \pm 0.9$ and $0.9 \pm 1.3$, respectively ($p = 0.07$). Usual care group had higher Aas score compared to educational group ($p = 0.048$). The total score of quality of life was $197.1 \pm 17.8$ in educational group and was $176.7 \pm 33.7$ in usual care group ($p = 0.009$). While none of the patients had emergency room application and hospital admission in educational group, seven patients had 21 emergency room application ($p = 0.01$) and four patients had four hospital admissions in usual care group. Additional short-acting inhaled $\beta_2$ agonist usage was found lower in the educational group ($p = 0.068$). In conclusion, proper drug use and usual care of patients are not sufficient for asthma treatment. Patient education is an important component of therapy in asthma patients. For a life with optimum standards, in addition to these factors, patient education must be accepted first by doctors and then by patients.

**Ambulatory Oxygen Improves Quality of Life of COPD Patients: A Randomised Controlled Study**—Eaton T, Garrett JE, Young P, Fergusson W, Kolbe J, Rudkin S, Whyte K. Eur Respir J 2002 Aug;20(2):306-312.

It is unknown whether acute response to ambulatory oxygen ($O_2$) predicts longer term improvement in health-related quality of life (HRQL) in chronic obstructive pulmonary disease (COPD) patients. The aims of this study were 1) to assess the short-term clinical impact, as determined by HRQL, of ambulatory $O_2$ in a 12-week, double-blind, randomised crossover study of $O_2$ (versus cylinder compressed air) of dyspnoeic but not chronically hypoxic COPD patients with exertional desaturation $\leq$ 88% (n=41), and 2) to determine whether either baseline characteristics or acute response to $O_2$ predicts short-term (12 weeks) response. Primary outcome measures were Chronic Respiratory Questionnaire (CRQ), Hospital Anxiety and Depression scale and the short form (SF)-36. Improvements were seen in all domains of the CRQ for cylinder O2 compared with cylinder air. Significant improvements were also noted in anxiety and depression and in certain domains of the SF-36. There were 28 (68%) acute responders to cylinder $O_2$ (defined as increase in 6-min walk $\geq$ 54 m or decrease in post-Borg dyspnoea $\geq$ 1) and 23 (56%) short-term responders (defined as clinically significant improvement in CRQ). However, acute and short-term responses were not correlated with no predictors of short-term response identified. At study completion, 14 (41%) of acute or short-term responders did not want to continue therapy, with 11 citing poor acceptability or tolerability. Short-term ambulatory oxygen is associated with significant improvements in health-related quality of life. These benefits cannot be predicted by baseline characteristics or acute response. Despite acute or short-term response, a substantial proportion of patients declined ambulatory oxygen.

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**Noninvasive Ventilation for Chest Wall and Neuromuscular Disorders**—Shneerson JM, Simonds AK. Eur Respir J 2002 Aug;20(2):480-487.

Neuromuscular and chest wall disorders are individually uncommon but together form an important group of conditions that can lead to chronic ventilatory failure. This is best recognised in scoliosis, kyphosis, following a thoracoplasty, in muscular dystrophies, such as Duchenne muscular dystrophy (DMD), and myotonic dystrophy, after poliomyelitis and with motor neurone disease (amyotrophic lateral sclerosis). If bulbar function is impaired, tracheostomy ventilation may be required, but in other situations, noninvasive ventilation is preferable. Positive pressure techniques using nasal and face masks are usually the first choice, but negative pressure ventilation is an alternative. There are no randomised-controlled trials regarding the indications for initiating noninvasive ventilation, but this is usually provided if there are symptoms due to nocturnal hypoventi-

lation or right heart failure in the presence of a raised carbon dioxide tension in arterial blood ($P_aCO_2$) either at night or, more usually, in the daytime as well. There is no evidence that "prophylactic" ventilatory support is of benefit if this is provided before ventilatory failure has appeared. Careful selection of patients is required, especially in the presence of progressive neuromuscular disorders such as DMD and motor neurone disease. There are no randomised-controlled trials concerning the outcome of noninvasive ventilation in these conditions, but studies have shown an improved quality of life, physical activity and haemodynamics, normalisation of blood gases and slight improvement in other physiological measures, such as the vital capacity and maximal mouth pressures. Survival in chest wall disorders is approximately 90% at 1 yr and 80% at 5 yrs, and similar figures have been obtained in nonprogressive neuromuscular conditions. If, however, the underlying disorder is deteriorating, particularly if it involves the bulbar muscles, it may limit survival despite the provision of adequate noninvasive ventilatory support.

**Stopping Smoking: A Prospective, Randomized, Double-Blind Study Comparing Nortriptyline to Placebo**—da Costa CL, Younes RN, Lourenco MT. Chest 2002 Aug;122(2):403-408.

OBJECTIVE: The administration of antidepressant drugs was shown to positively affect the rate of smoking cessation. This study evaluates the efficacy of nortriptyline in an antismoking program. METHODS: A possible randomized double-blind study that included 144 patients who were randomized to receive nortriptyline, 75 mg/d (68 patients), or placebo (76 patients), during 6 consecutive weeks. All patients attended behavioral group orientation for 5 weeks. The rate of success, complications, adherence to the regime, and factors of pretreatment prognosis were evaluated (multivariate analysis). RESULTS: The groups were balanced in relation to the characteristics of the patients on entering the study. Patients receiving nortriptyline showed significantly higher cessation rate (55.9%) compared to the group receiving placebo (23.3%; $p < 0.001$). In a univariate analysis on prognosis factors influencing the rate of cessation in our study, the Fagerstrom test results ($p = 0.005$) and nortriptyline ($p < 0.001$) were identified. Logistic regression showed that a Fagerstrom test score of < 7 (odds ratio [OR], 3.1; 95% confidence interval [CI], 1.47 to 6.7; $p = 0.003$) and nortriptyline use (OR, 4.1; 95% CI, 2 to 8.3; $p < 0.001$) were independent factors impacting the rate of success for smoking cessation. No significant complications were observed in the nortriptyline group. CONCLUSION: This study showed that nortriptyline significantly increases the smoking cessation rate in chronic smokers, as compared to the placebo group, without any significant side effects.

**IV Magnesium Sulfate in the Treatment of Acute Severe Asthma: A Multicenter Randomized Controlled Trial**—Silverman RA, Osborn H, Runge J, Gallagher EJ, Chiang W, Feldman J, et al; Acute Asthma/Magnesium Study Group. Chest 2002 Aug;122(2):489-497.

BACKGROUND: Studies of IV magnesium sulfate as a treatment for acute asthma have had mixed results, with some data suggesting a benefit for acute severe asthma, but not for mild-to-moderate asthma. In a multicenter cohort, this study tests the hypothesis that administration of magnesium sulfate improves pulmonary function in patients with acute severe asthma. DESIGN: Placebo-controlled, double-blind, randomized clinical trial. SETTING: Emergency departments (EDs) of eight hospitals. PATIENTS: Patients aged 18 to 60 years presenting with acute asthma and $FEV_1 \leq 30\%$ predicted on arrival to the ED. INTERVENTION: All patients received nebulized albuterol at regular intervals and IV methylprednisolone. Two grams of IV magnesium sulfate or placebo were administered 30 min after ED arrival. The primary efficacy end point was $FEV_1$ at 240 min, and the data analysis was intent to treat. RESULTS: Two hundred forty-eight patients were included, and the mean $FEV_1$ on ED arrival was 22.9% predicted. At 240 min, patients receiving magnesium had a mean $FEV_1$ of 48.2% predicted, compared to 43.5% predicted in the placebo-treated group (mean difference, 4.7%; 95% confidence interval [CI], 0.29 to 9.3%; $p = 0.045$). A regression model confirmed the effect of magnesium compared to placebo was greater in patients with a lower initial $FEV_1$ ($p < 0.05$). If the initial $FEV_1$ was < 25% predicted, the final $FEV_1$ was 45.3% predicted in the magnesium-treated group and 35.6% predicted in the placebo-treated group (mean difference, 9.7%; 95% CI, 4.0 to 15.3%; $p = 0.001$). If the initial FEV was ≥ 25% predicted, magnesium administration was not beneficial; the final $FEV_1$ was 51.1% predicted in the magnesium-treated group and 53.9% predicted in the placebo-treated group (mean difference, - 2.9%, 95% CI, - 9.4 to 3.7; p = not significant). Overall, the use of magnesium sulfate did not improve hospital admission rates. CONCLUSION: Administration of 2 g of IV magnesium sulfate improves pulmonary function when used as an adjunct to standard therapy in patients with very severe, acute asthma.

**Hospital Initiatives in Promoting Smoking Cessation: A Survey of Internet and Hospital-Based Programs Targeted at Consumers**—Denny JT, Ginsberg S, Papp D, Browne G, Morgan S, Kushins L, Solina A. Chest 2002 Aug;122(2):692-698.

STUDY OBJECTIVES: This study assesses how often local US hospitals provide smoking cessation information in the following two ways: via hospital Web sites; and via routing incoming phone calls to their hospital switchboards to an in-house smoking cessation clinic. DESIGN: Random survey of US hospitals. SETTING: US hospital Web pages and telephone switchboards. Patients or participants: One hundred two randomly selected US hospitals. INTERVENTIONS: One hundred two hospital Web sites were randomly selected across the United States. The site was searched for the topic of smoking cessation. In the second phase of the survey, the main switchboard number of the same 102 hospitals was anonymously called and the "stop smoking clinic" was asked for. MEASUREMENTS AND RESULTS: The overall results indicate that among the hospital Web sites surveyed, only 30% contained information relating to smoking cessation programs. The phone survey of hospital switchboards showed that 47% had a smoking cessation program available via phone inquiry, while 53% did not. CONCLUSIONS: Of the US hospital Web sites visited, only 30% contained information on smoking cessation. The yield of finding the desired information was increased by the presence of an intrasite search option, which is a low-cost enhancement to any complex Web site. The relatively low cost of promoting healthy behaviors such as smoking cessation on a hospital Web site should be used more widely. Surprisingly, the phone survey of hospitals showed that the lower technology route of providing smoking cessation information to patients via a patient-initiated phone call is only available in 47% of hospitals. Both the Internet and phone-based switchboard referrals could be more widely and effectively used. Joint Commission on Accreditation of Healthcare Organizations guidelines would be one avenue of increasing the availability of smoking cessation information at hospital switchboards and Web sites.

**A Randomised Controlled Crossover Trial of Nurse Practitioner Versus Doctor Led Outpatient Care in a Bronchiectasis Clinic**—Sharples LD, Edmunds J, Bilton D, Hollingworth W, Caine N, Keogan M, Exley A. Thorax 2002 Aug;57(8):661-666.

BACKGROUND: With the decrease in junior doctor hours, the advent of specialist registrars, and the availability of highly trained and experienced nursing personnel, the service needs of patients with chronic respiratory diseases attending routine outpatient clinics may be better provided by appropriately trained nurse practitioners. METHODS: A randomised controlled crossover trial was used to compare nurse practitioner led care with doctor led care in a bronchiectasis outpatient clinic. Eighty patients were recruited and randomised to receive 1 year of nurse led care and 1 year of doctor led care in random order. Patients were followed up for 2

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years to ensure patient safety and acceptability and to assess differences in lung function. Outcome measures were forced expiratory volume in 1 second ($FEV_1$), 12 minute walk test, health related quality of life, and resource use. RESULTS: The mean difference in $FEV_1$ was 0.2% predicted (95% confidence interval -1.6 to 2.0%, p=0.83). There were no significant differences in the other clinical or health related quality of life measures. Nurse led care resulted in significantly increased resource use compared with doctor led care (mean difference pound 1497, 95% confidence interval pound 688 to pound 2674, p<0.001), a large part of which resulted from the number and duration of hospital admissions. The mean difference in resource use was greater in the first year ( pound 2625) than in the second year ( pound 411). CONCLUSIONS: Nurse practitioner led care for stable patients within a chronic chest clinic is safe and is as effective as doctor led care, but may use more resources.

**Distal Projection of Insufflated Gas During Tracheal Gas Insufflation**—Carter CS, Hotchkiss JR, Adams AB, Stone MK, Marini JJ. J Appl Physiol 2002 May;92(5):1843-1850.

Tracheal gas insufflation (TGI) flushes expired gas from the ventilator circuitry and central airways, augmenting $CO_2$ clearance. Whereas a significant portion of this washout effect may occur distal to the injection orifice, the penetration and mixing behavior of TGI gas has not been studied experimentally. We examined the behavior of 100% oxygen TGI injected at set flow rates of 1-20 L/min into a simulated trachea consisting of a smooth-walled, 14-mm-diameter tube. Models incorporating a separate coaxial TGI injector, a rough-walled trachea, and a bifurcated trachea were also studied. One-hundred percent nitrogen, representing expiratory flow, passed in the direction opposite to TGI at set flow rates of 1-25 L/min. Oxygen concentration within the "trachea" was mapped as a function of axial and radial position. Three consistent findings were observed: 1) mixing of expiratory and TGI gases occurred close to the TGI orifice; 2) the oxygenated domain extended several centimeters beyond the endotracheal tube, even at high-expiratory flows, but had a defined distal limit; and 3) more distally from the site of gas injection, the TGI gas tended to propagate along the tracheal wall, rather than as a central projection. We conclude that forward-directed TGI penetrates a substantial distance into the central airways, extending the compartment susceptible to $CO_2$ washout.

**Mechanical Ventilation Results in Progressive Contractile Dysfunction in the Diaphragm**—Powers SK, Shanely RA, Coombes JS, Koesterer TJ, McKenzie M, Van Gammeren D, et al. J Appl Physiol 2002 May;92(5):1851-1858.

These experiments tested the hypothesis that a relatively short duration of controlled mechanical ventilation (MV) will impair diaphragmatic maximal specific force generation (specific $P_o$) and that this force deficit will be exacerbated with increased time on the ventilator. To test this postulate, adult Sprague-Dawley rats were randomly divided into one of six experimental groups: 1) control (n = 12); 2) 12 h of MV (n = 4); 3) 18 h of MV (n = 4); 4) 18 h of anesthesia and spontaneous breathing (n = 4); 5) 24 h of MV (n = 7); and 6) 24 h of anesthesia and spontaneous breathing (n = 4). MV animals were anesthetized, tracheostomized, and ventilated with room air. Animals in the control group were acutely anesthetized but were not exposed to MV. Animals in two spontaneous breathing groups were anesthetized and breathed spontaneously for either 18 or 24 h. No differences ($p > 0.05$) existed in diaphragmatic specific $P_o$ between control and the two spontaneous breathing groups. In contrast, compared with control, all durations of MV resulted in a reduction ($p < 0.05$) in diaphragmatic specific tension at stimulation frequencies ranging from 15 to 160 Hz. Furthermore, the MV-induced decrease in diaphragmatic specific $P_o$ was time dependent, with specific $P_o$ being approximately 18 and approximately 46% lower ($p < 0.05$) in animals mechanically ventilated for 12 and 24 h, respectively. These data support the hypothesis that relatively short-term MV impairs diaphragmatic contractile function and that the magnitude of MV-induced force deficit increases with time on the ventilator.

**The Relatinn Between the Availability of Neonatal Intensive Care and Neonatal Mortality**—Goodman DC, Fisher ES, Little GA, Stukel TA, Chang CH, Schoendorf KS. N Engl J Med 2002 May 16;346(20):1538-1544.

BACKGROUND: There is marked regional variation in the availability of neonatal intensive care in the United States. We conducted a study to determine whether a greater supply of neonatologists or neonatal intensive care beds is associated with lower neonatal mortality. METHODS: We used the 1996 master files of the American Medical Association and the American Osteopathic Association and 1998 and 1999 surveys of neonatal intensive care units to calculate the supply of neonatologists and neonatal intensive care beds in 246 neonatal intensive care regions. We used linked birth and death records from the 1995 U.S. birth cohort to assess associations between the supply of both neonatologists and neonatal intensive care beds per capita (in quintiles) and the risk of death within the first 27 days of life. RESULTS: Among 3,892,208 newborns with a birth weight of 500 g or greater, the mortality rate was 3.4 per 1000 births. After adjustment for neonatal and maternal characteristics associated with an increased risk of neonatal death, the rate was lower in the regions with 4.3 neonatologists per 10,000 births than in those with 2.7 neonatologists per 10,000 births (odds ratio for death, 0.93; 95 percent confidence interval, 0.88 to 0.99). Further increases in the number of neonatologists were not associated with greater reductions in the risk of death. There was no consistent relation between the number of neonatal intensive care beds and neonatal mortality. CONCLUSIONS: A minority of regions in the United States may have inadequate neonatal intensive care resources, whereas many others may have more resources than are needed to prevent the death of high-risk newborns. The effect of the availability of neonatologists on other health outcomes is not known.

**Alcohol-Based Handrub Improves Compliance with Hand Hygiene in Intensive Care Units**—Hugonnet S, Perneger TV, Pittet D. Arch Intern Med 2002 May 13;162(9):1037-1043.

BACKGROUND: Nosocomial infection is a leading complication in intensive care units. Although hand hygiene is the single most efficient preventive measure, compliance with this simple action remains low. OBJECTIVES: To assess the effect of an intervention to promote hand hygiene and to investigate risk factors for noncompliance in intensive care units. METHODS: We performed 7 observational surveys and implemented a promotional campaign after baseline in medical, surgical, and pediatric intensive care units of a teaching hospital. Health care workers were observed during routine patient care. The intervention consisted of a hospitalwide promotional campaign, including observation and performance feedback, posters display, and distribution of individual bottles of alcohol-based handrub. The main outcome measure was compliance with hand hygiene through handwashing or handrubbing. RESULTS: We observed 2743 opportunities for hand hygiene distributed over 248 periods. Overall compliance increased from 38.4% to 54.5% during the study ($p< 0.001$). Although recourse to handwashing remained stable at around 30%, handrubbing increased from 5.4% at baseline to 21.7% at the last survey ($p< 0.001$). Compliance increased among nurses and nursing assistants, but remained stable among physicians. Handwashing compliance decreased, on average, by 4.7% for an increase of 10 opportunities for hand hygiene per hour of patient care ($p< 0.001$), whereas no such association existed for handrubbing. CONCLUSIONS: Our intervention induced a marked and sustained increase in compliance with hand hygiene. In intensive care units, less time-consuming handrubbing might replace standard handwashing and overcome the barrier of time constraints.

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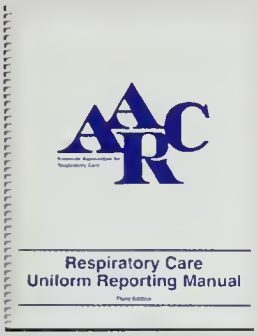


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**Endothelial Responses to Mechanical Stress: Where Is the Mechanosensor?**—Ali MH, Schumacker PT. Crit Care Med 2002 May;30(5 Suppl):S198-S206.

OBJECTIVE: The endothelium is normally subjected to mechanical deformation resulting from shear stress and from strain associated with stretch of the vessel wall. These stimuli are detected by a mechanosensor that initiates a variety of signaling systems responsible for triggering the functional responses. The identity of the mechanosensor has not been established. This article discusses the different mechanisms of mechanosensing that have been proposed and reviews the literature with respect to signaling systems that are activated in response to stress and strain in endothelium. DATA SOURCES: Published literature related to mechanotransduction, signal transduction pathways initiated by strain in endothelium, and pathophysiologic effects of abnormal shear forces in diseases. DATA EXTRACTION AND SYNTHESIS: Proposed mechanisms of mechanosensing include stretch-sensitive ion channels, protein kinases associated with the cytoskeleton, integrin-cytoskeletal interactions, cytoskeletal-nuclear interactions, and oxidase systems capable of generating reactive oxygen species. However, the molecular identity of the mechanosensor is not known, nor is it clear whether multiple sensing mechanisms exist. CONCLUSIONS: Many responses are initiated in cells subjected to mechanical deformation, including alterations in ion channel conductance, activation of signal transduction pathways, and altered expression of specific genes. Future progress in this field will require a critical distinction between cell systems that become activated during mechanical strain and the identity of the cellular mechanosensor that triggers subsequent responses.

**Shear Stress and Endothelial Cell Activation**—Fisher AB, Al-Mehdi AB, Manevich Y. Crit Care Med 2002 May;30(5 Suppl):S192-S197.

We have shown previously that ischemia in an isolated rat lung that is normally oxygenated by continued ventilation results in lipid and protein oxidation, indicating the generation of reactive oxygen species. By using a variety of biochemical and imaging techniques, we determined that the initial response, which occurs within the first second of ischemia, is partial depolarization of the endothelial cell plasma membrane. This event is followed within several seconds by activation of endothelial NADPH oxidase and generation of superoxide anion at the extracellular surface of the cell membrane where it is dismutated to freely diffusible $H_2O_2$. Approximately 15 secs after the onset of ischemia, we detected an elevation of intracellular Ca2+ caused by its release from intracellular stores, followed by Ca2+ influx, possibly through T-type voltage-dependent Ca2+ channels. Increased nitric oxide generation through activation of endothelial nitric oxide synthase is detected after about 45 secs of ischemia. These changes (endothelial membrane depolarization, reactive oxygen species production, elevation of intracellular Ca2+ levels, and nitric oxide generation) were confirmed in isolated endothelial cells that had been adapted to shear stress in vitro. The in vitro model also demonstrates reactive oxygen species-dependent activation of nuclear factor-kappaB and activator protein-1 and that 24 hrs of ischemia results in increased cell division. These results indicate a novel cell-signaling pathway in response to loss of shear stress. The basis for these changes in endothelial function is related to mechanotransduction, i.e., altered shear stress rather than a metabolic response to ischemia. The biological function for the response may be an attempt to restore blood flow through vasodilatation and new capillary formation.

**Short-Term Acupuncture Therapy Is of No Benefit in Patients with Moderate Persistent Asthma**—Shapira MY, Berkman N, Ben-David G, Avital A, Bardach E, Breuer R. Chest 2002 May;121(5):1396-1400.

STUDY OBJECTIVES: Acupuncture traditionally has been used to treat asthma. Nevertheless, only a few controlled studies have been performed to determine the efficacy of this treatment. Our study aimed to determine the efficacy of acupuncture in patients with moderate persistent asthma. METHODS: Twenty-three patients with moderate persistent asthma who had been treated only with inhaled $ß_2$-agonists were randomly assigned to receive four sessions of real acupuncture (RA) or sham acupuncture (SA) in a blinded manner. After a washout period of 3 weeks, the patients were crossed over. Monitoring included $FEV_1$, methacholine challenge, daily peak flow (PF) variability, and the keeping of an asthma diary. RESULTS: Twenty of 23 patients completed the study. There was no significant change in $FEV_1$ following treatment. The mean ± SE) $FEV_1$ values before and after the RA were 73 ± 4% and 73 ± 3%, respectively (not significant [NS]). $FEV_1$ values before and after SA were 70 ± 3% and 70 ± 3%, respectively (NS). There was also no change in provocative methacholine concentration causing a 20% fall in $FEV_1$ ($PC_{20}$) before and after treatment. The mean $PC_{20}$ values before and after RA were 0.92 ± 0.42 mg/mL and 1.16 ± 0.51 mg/mL, respectively (p = 0.71), while the $PC_{20}$ values before and after SA were 1.47 ± 0.83 mg/mL and 1.11 ± 0.79 mg/mL, respectively (p = 0.59). There was no change in the mean PF variability before and after the RA (1.6 ± 3.1% and 1.8 ± 2.3%, respectively [NS]). The PF variability before and after SA were 3.6 ± 2.8% and 2.8 ± 3.4%, respectively (NS). No significant difference was demonstrated for symptom scores or for the use of $ß_2$-agonist inhalers (RA, 6.7 ± 3.4; SA, 8.1 ± 3.6; p = 0.58). CONCLUSION: In patients with moderate persistent asthma, a short course of acupuncture treatment resulted in no change in lung functions, bronchial hyperreactivity, or patient symptoms.

**Comparison of the Effects of Salmeterol and Formoterol in Patients with Severe Asthma**—Nightingale JA, Rogers DF, Barnes PJ. Chest 2002 May;121(5):1401-1406.

STUDY OBJECTIVE: Several studies have demonstrated the superiority of salmeterol and formoterol to either regular treatment with albuterol or placebo. However, to date there have been no trials comparing the efficacy of salmeterol and formoterol in patients with severe asthma. DESIGN: We undertook a randomized, placebo-controlled, crossover study to compare 4 weeks of treatment with inhaled formoterol (12 microg twice daily) or salmeterol (50 microg twice daily) in patients with severe asthma whose conditions were not being adequately controlled by therapy with high doses of inhaled corticosteroids (i.e., ≥ 1,500 microg daily) or with regular oral corticosteroid treatment. Morning pretreatment peak expiratory flow (PEF) during the last 14 days of the treatment period was the primary outcome variable. Patients recorded morning and evening pretreatment PEF, daytime and nighttime symptom scores, and any use of rescue medication. Spirometry and bronchial reversibility were performed after each treatment. RESULTS: Forty-two nonsmoking patients (29 women; mean age, 45 ± 2 years; mean [± SEM] $FEV_1$, 61.8 ± 3.4% of predicted) took part in the trial, and 27 patients completed the trial. The mean morning PEF was greater in patients receiving formoterol (mean increase, 14.4 L/min; 95% confidence interval [CI], 0.2 to 28.6) or salmeterol (mean increase, 14.8 L/min; 95% CI, 0.5 to 29.1) compared with those receiving placebo, but there was no difference between these treatments. There were no significant treatment effects for any of the secondary outcome variables (i.e., $FEV_1$ FVC, mean evening PEF, mean daytime symptom score, or nighttime symptom score). CONCLUSION: We conclude that the long-acting $ß_2$-agonists salmeterol and formoterol improve morning PEF in patients with severe asthma, but that there is no difference in efficacy between the two drugs.

**Near-Fatal Asthma: A Population-Based Study of Risk Factors**—Mitchell I, Tough SC, Semple LK, Green FH, Hessel PA. Chest 2002 May;121(5):1407-1413.

BACKGROUND: The study of near-fatal asthma (NFA) may provide a means to further our understanding of fatal asthma. Studies of NFA often are derived from a single ICU rather than from a defined population. We therefore aimed to identify factors distinguishing NFA patients (cases) from those persons treated in an emergency department (ED) [ED control subjects] and in the community (community control subjects [CCs]). METHODS: This was a population-based case-control study conducted over 20 months of 45 NFA patients (age range, 5 to 50 years), 197 ED control subjects treated in an ED, and 303 CCs, all of whom were residents of Alberta. RESULTS: The age distribution was similar between NFA patients and control subjects, with the majority being < 22 years of age (NFA patients, 68.9%; ED control subjects, 71.3%; CCs, 60.7%). Those patients with NFA were significantly more likely to have received a diagnosis before 5 years of age (66.6%), compared to ED control subjects (39.6%) and CCs (28.7%). The NFA group was significantly more likely to report moderate-to-severe disease and more frequent symptoms than the other groups. Therapy with bronchodilators was used most frequently by the NFA group compared to the ED control subjects and CCs ($p < 0.001$), as was therapy with inhaled steroids ($p < 0.001$) and oral steroids ($p < 0.001$). NFA patients had higher scores for vulnerability and were most likely to admit to stress as an asthma trigger. All groups had high exposure to cigarette smoke and pets. CONCLUSION: NFA patients have many modifiable risk factors and many similarities to ED control subjects and CCs with asthma. General measures to improve asthma control and awareness of risks are required in all groups.

**Cough and Phlegm Are Important Predictors of Health Status in Smokers Without COPD**—Heijdra YF, Pinto-Plata VM, Kenney LA, Rassulo J, Celli BR. Chest 2002 May;121(5):1427-1433.

STUDY OBJECTIVES: The health-related quality of life of smokers without COPD and that of ex-smokers has not been defined. If abnormal, the role of small airways disease and that of cough and phlegm have never been evaluated. Therefore, the aim of the study was to explore whether the differences in quality of life between smokers and ex-smokers could be explained by cough and phlegm, differences in pulmonary function tests, or exercise capacity. DESIGN: Observational, prospective. SETTING: Pulmonary and Critical Care Division, COPD Center at St. Elizabeth's Medical Center. POPULATION: In 36 smokers, 21 ex-smokers (stopped smoking for > 20 years), 19 never-smokers with normal FVC and $FEV_1$ values, and 41 patients with COPD ($FEV_1$ 38 ± 11% predicted [mean ± SD]), the St. George's Respiratory Questionnaire (SGRQ), pulmonary function tests, and a 6-min walk distance (6MWD) were performed. RESULTS: The total SGRQ scores were worse in current smokers (15 ± 15) than in ex-smokers (6 ± 4) or never-smokers (4 ± 3) [$p < 0.05$]. As expected, the worst score was seen in COPD (50 ± 15). After correcting for cough and phlegm, the difference in SGRQ scores between smokers and ex-smokers disappeared. In current and ex-smokers, the SGRQ score was associated with the exposure to pack-years smoking history ($r = 0.45$, $p < 0.01$, and $r = 0.83$, $p < 0.0001$, respectively) but independent of lung function or exercise parameters (6MWD). CONCLUSIONS: In smokers without COPD, the abnormal SGRQ score is due to the noxious effect of cigarette smoke, resulting in cough and phlegm, independent of its physiologic effects.

**Significance of Abnormal Chest Radiograph Findings in Patients with HIV-1 Infection Without Respiratory Symptoms**—Gold JA, Rom WN, Harkin TJ. Chest 2002 May;121(5):1472-1477.

STUDY OBJECTIVES: Patients with HIV-1 infection or AIDS may present with abnormal chest radiograph (CXR) findings in the absence of symptoms specific to the lung. The objective was to determine the spectrum of disease and the diagnostic modalities employed in these patients. METHODS: From 1996 to 1998, we identified patients with HIV-1 infection presenting to the Bellevue Hospital Chest Service with abnormal CXR findings, and absence of specific pulmonary symptoms. Charts were reviewed for presence of constitutional symptoms, CD4 lymphocyte count, use of Pneumocystis carinii pneumonia (PCP) prophylaxis, eventual diagnosis, and all diagnostic modalities employed. CXR findings were classified according to their predominant abnormalities: nodules, infiltrates, cavity, mass, adenopathy, or effusion. RESULTS: Forty-four patients were eligible for inclusion. Eight-six percent of patients had a CD4 lymphocyte count < 200 cells/microL, and 57% were receiving PCP prophylaxis. Nodular disease was the most common radiographic abnormality (57%), followed by adenopathy (17%). A definitive diagnosis was obtained in 86% of the patients. The most common diagnosis was tuberculosis (26%), followed by nontuberculous mycobacteria (NTM, 23%) and Kaposi sarcoma (12%). No patients had PCP or bacterial pneumonia. Sixty-two percent of patients required an invasive modality to establish a diagnosis. Only 18% of patients with tuberculosis (2 of 11 patients) received diagnoses by sputum analysis. CONCLUSIONS: Patients with HIV-1 infection, abnormal CXR findings, and lack of pulmonary symptoms have a high incidence of infectious disorders, especially pulmonary tuberculosis and infection due to NTM. The high prevalence of treatable and potentially communicable disorders warrants an aggressive diagnostic approach in these patients.

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Part II of Two Special Issues

# Liquid Nebulization: Emerging Technologies

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Containing the papers and discussions from the 30th RESPIRATORY CARE Journal Conference

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Conference faculty members—front row, from left: Joseph L Rau PhD RRT FAARC, Dean R Hess PhD RRT FAARC, Myrna B Dolovich PEng, Neil R MacIntyre MD FAARC, Gerald C Smaldone MD PhD, Thomas G O'Riordan MD. Back row, from left: Alessandro Gomez PhD, Rajiv Dhand MD, Patrick J Dunne MEd RRT FAARC, Peter W Barry MD, Bruce K Rubin MD MEng FAARC, David E Geller MD, John H Dennis PhD MSc. Not pictured: Robert J Meyer MD.

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Bradford, United Kingdom

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Columbia, Missouri

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Hamilton, Ontario, Canada

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Fullerton, California

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Orlando, Florida

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Atlanta, Georgia

Bruce K Rubin MD MEng FAARC
Winston-Salem, North Carolina

Gerald C Smaldone MD PhD
Stony Brook, New York

# DISCUSSANTS

Elna Berg
Lund, Sweden

Stanley B Fiel MD
Philadelphia, Pennsylvania

James B Fink MSc RRT FAARC
Mountain View, California

Carolyn McMahon
Riverside, California

Alex Stenzler RPFT
Yorba Linda, California

Theodore J Witek Jr DrPH RRT FAARC
Ingelheim am Rhein, Germany

# New Liquid Aerosol Generation Devices: Systems That Force Pressurized Liquids Through Nozzles

David E Geller MD

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Summary

**Over the past few decades, aerosol delivery devices have been relatively inefficient, wasteful, and difficult for patients to use. These drawbacks have been tolerated because the drugs available for inhalation have wide therapeutic margins and steep dose-response curves at low doses. Recently several forces have converged to drive innovation in the aerosol device industry: the ban on chlorofluorocarbon propellants in metered-dose inhalers, the need for more user-friendly devices, and the invention of expensive inhalable therapies for topical and systemic lung delivery. Numerous devices are in development to improve the efficiency, ease of use, and reproducibility of aerosol delivery to the lung, including systems that force liquid through a nozzle to form the aerosol cloud. The Respimat is a novel, compact, propellant-free, multi-dose inhaler that employs a spring to push drug solution through a nozzle, which generates a slow-moving aerosol. Deposition studies show that the Respimat can deliver 39–44% of a dose to the lungs. Clinical asthma and chronic obstructive pulmonary disease trials with bronchodilators show that the Respimat is 2–8 times as effective as a metered-dose inhaler. Respimat has been tested with bronchodilators and inhaled corticosteroids. The AERx device uses sophisticated electronics to deliver aerosol from a single-dose blister, using an integral, disposable nozzle array. The electronics control dose expression and titration, timing of aerosol generation with the breath, and provide feedback for proper inhalation technique. Lung deposition ranges from 50 to 80% of the loaded dose, with remarkable reproducibility. AERx has been tested with a variety of drugs, for both topical and systemic delivery, including rhDNase (dornase alfa), insulin, and opioids. These novel devices face competition from other technologies as well as financial and regulatory hurdles, but they both offer a marked improvement in the efficiency of pulmonary drug delivery.** *Key words: nebulizer, nebulization, aerosol, AERx, Respimat.* [Respir Care 2002;47(12):1392–1404]

## Introduction

For the past half century the devices available for the delivery of aerosolized drugs to the lung have included pressurized metered-dose inhalers (pMDIs), jet and ultrasonic nebulizers, and dry powder inhalers (DPIs). Each of these systems has benefits and drawbacks with respect to the type of drug used and the target patient population. The well-recognized inefficiencies of these devices[1] have not been of concern until recently, since most of the aerosolized drugs for topical lung delivery (ie, bronchodilators and anti-inflammatory agents) are inexpensive and have wide therapeutic margins. However, over the past decade there have been many driving forces for the innovation of new inhalable drug formulations and devices to deliver them.

First, the ban on chlorofluorocarbon (CFC) (to preserve the upper atmosphere's ozone layer) has required pharmaceutical companies to seek alternative propellants. The pMDI has for decades been one of the most commonly prescribed delivery methods for asthma and chronic obstructive pulmonary disease (COPD) drugs, so the ban on CFC is a major driving force for change in the industry. The basic design of the pMDI is almost 50 years old, with few modifications until recently. The pMDI was a landmark innovation that has had tremendous impact on inhaled drug delivery, though the problems with its use are well known.[1] The pMDI is relatively difficult to teach and to use and requires synchronization of actuation and inhalation to achieve successful lung deposition. Pressurized MDIs produce high-velocity particles that impact in the oropharynx and cause adverse effects. Drug delivery to the lung with CFC pMDIs is only 5–20% of the label dose, even with good technique. Children under a few years old are incapable of mastering the pMDI technique. To overcome these difficulties, several companies designed spacers and valved holding chambers to reduce oropharyngeal deposition and improve coordination. The competition between the companies that manufacture spacers led to a huge body of literature arguing the merits of the various devices, leading to confusion among clinicians and patients.

Alternatives to the CFC pMDI include other propellants, such as hydrofluoroalkane (HFA), new DPIs, and the recently developed propellant-free liquid systems. The HFA pMDIs have been redesigned to solve some of the problems with the CFC devices. The plume has a slower velocity, there is no "cold FREON" effect, and the last few doses in the canister are delivered more consistently. Some of the inhaled corticosteroids are soluble in the HFA propellant/excipient mixture and have been engineered to deliver small-particle aerosols (average droplet size of only 1 $\mu$m), which improves lung deposition and decreases throat deposition.[2] Other HFA formulations have particle size characteristics similar to their inefficient CFC counterparts. Like CFC pMDIs, HFA pMDIs require synchronization of the actuation and the inspiratory effort, so holding chambers may be necessary for some patients. DPIs are also available for many medications and come in single-dose and multiple-dose formats. DPIs are breath-actuated and rely on the patient's inspiratory effort to deaggregate the powder into fine particles that can be deposited in the lung. DPI deposition efficiency is in the range of approximately 12–37%, depending on the device, the formulation, and the patient.[3] Since a stronger inspiratory effort is required with current DPIs, there is substantial oropharyngeal deposition. The difficulties with pMDIs and DPIs are partly responsible for the development of propellant-free liquid aerosol systems.

Another force driving innovation of new aerosol technology is the recognition that existing devices are either inefficient, difficult to use, or have poor precision (high intra-subject and inter-subject variability). In addition to the above-described problems with pMDIs and DPIs, jet and ultrasonic nebulizers waste drug by having large dead volumes (ie, medication remaining in the nebulizer after nebulization has ceased), by nebulizing during exhalation, and by forming polydisperse aerosols that have a high percentage of droplets too large to reach the lung. With most of the available systems the patient is not guided or prompted to breathe in an appropriate or consistent fashion, which increases variability of lung deposition. Drugs with large therapeutic windows, such as anti-inflammatories, $\beta_2$ agonists, and anticholinergics, can be clinically effective even when delivered by inefficient devices, but more recent medications and novel therapies in development, including gene therapies, are too expensive to tolerate substantial waste.

Nebulizers are the most time-consuming method of aerosol delivery. Patients with cystic fibrosis (CF) and other chronic lung diseases may have numerous aerosol medications to use, which may take up to 2 hours daily. New user-friendly devices that reduce treatment time may improve patient compliance with therapy and thus improve outcomes and quality of life.

Finally, the need for novel device development has been fueled by the invention of innovative liquid formulations and modifications of older formulations designed to use

David E Geller MD is affiliated with the Aerosol Research Laboratory and Cystic Fibrosis Center, The Nemours Children's Clinic, Orlando, Florida.

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Correspondence: David E Geller MD, The Nemours Children's Clinic, 83 W Columbia Street, Orlando FL 32806. E-mail: dgeller@nemours.org.

the large absorptive surface of the peripheral lung as a portal for systemic drug delivery. These therapies include peptides, proteins, small molecules, hormones, and liposome/drug suspensions. Many of these agents have a very narrow therapeutic index and require a marked improvement in efficiency and precision of dosing to the distal lung. DPIs with drugs reformulated into easily dispersible powders with improved aerodynamic properties have been used for systemic drug delivery via inhalation (eg, by Inhale Therapeutics). However, for most novel drugs, liquid formulations are used as a starting point for development.[4] Many formulations have already been used as parenteral solutions or suspensions, with known storage and stability variables. The aerosol characteristics of an aqueous compound are mostly controlled by the device design, not by the inhalation pattern. Feasibility studies to demonstrate the usefulness of inhaling a compound can proceed more quickly with liquid formulations. The new devices must optimize aerosol delivery to the peripheral lung, which maximizes the absorption of drug into the bloodstream and minimizes drug loss by mucociliary transport. Also, the intra-subject and inter-subject variability of pharmacokinetic variables should be comparable to those of conventional methods.

The new aerosol systems developed for systemic drug delivery are so efficient that many have been modified for use with topical airway drugs as well. Improved design features of the new devices include smaller device size to improve portability, a flow sensor to match bolus drug delivery to the breathing pattern, and features that guide the patient to inhale at the proper flow rate. These improvements should improve dosing reliability and patient acceptance.

## New Liquid Aerosol Generators

Some of the recently introduced devices are improved versions of jet nebulizer technology.[4] For example, the AeroEclipse (Monaghan Medical, Syracuse, New York) is a compressor-driven, breath-actuated nebulizer. The breath actuation is controlled by a mechanical spring device and helps minimize drug waste during exhalation. The HaloLite (Profile Therapeutics, West Sussex, United Kingdom) is also a breath-actuated nebulizer; it uses adaptive aerosol delivery to electronically monitor the patient's breathing pattern, then delivers a pulse of aerosol to the first 50% of each inhalation. A pre-set dose is delivered with each button push of the HaloLite system. The AKITA (InAMed, München-Gauting, Germany) delivery system incorporates conventional jet nebulizers, but directs the patient to take slow, deep breaths and only delivers aerosol during inhalation. These devices match drug output to the patient's respiratory pattern, may increase lung dose, and minimize drug waste during exhalation, breath-holding, coughing, or talking. However, they do have substantial dead volume.

Other new devices create aerosol by way of a porous membrane that vibrates at ultrasonic frequencies. Examples include Aeroneb, Aerodose (Aerogen, Mountain View, California), the Omron ultrasonic nebulizer (Omron, Tokyo, Japan), and the eFlow (PARI, Starnberg, Germany). Electrospray aerosol generators, such as that under development at BattellePharma (Columbus, Ohio), create a nearly monodisperse, low-velocity aerosol from a liquid. These new-generation devices are discussed in the other reviews in this issue of Respiratory Care. The remainder of this review discusses the Respimat and AERx, 2 new devices that produce an aerosol by forcing liquids through nozzles.

## Devices That Create an Aerosol by Forcing Liquids Through Nozzles

The technique of forcing liquid through a nozzle to create an aerosol is not new. In the late 19th century, antiseptics were nebulized by this method to treat tuberculosis. In the early 1900s Ephraim used adrenaline in a perfume atomizer to treat asthma and laryngeal edema.[5] Nasal spray bottles also use systems that force the drug suspension through a nozzle. In his contribution to this Journal Conference published in the previous issue of Respiratory Care, Dr MacIntyre described a new type of aerosol generator: a multi-channel catheter that passes through an endotracheal tube and generates the aerosol at the catheter tip, within the trachea.

## The Respimat

The Respimat (Boehringer Ingelheim, Ingelheim am Rhein, Germany) is a novel, propellant-free, hand-held, multi-dose inhaler that has the convenience of a pMDI but offers better particle characteristics and ease of use (Fig. 1). Application for regulatory approval of the Respimat will be submitted in Germany and other countries soon.

The Respimat generates a slow-moving aerosol ("soft mist") from a metered dose of drug, using the mechanical power of a spring. The qualities of the aerosol produced are not dependent on propellants or inspiratory effort (unlike pMDIs and DPIs, respectively). The Respimat does not require a spacer, battery, or outside electric power source. The liquid in the cartridge is a solution, not a suspension, so no shaking is required. The Respimat is reusable for the life of 3 replacement cartridges.

Figure 2 shows a diagram of the Respimat. The patient primes the device by rotating the base 180 degrees, which

Fig. 1. The Respimat soft-mist inhaler. (Courtesy of Boehringer Ingelheim, Ingelheim am Rhein, Germany.)

(1) compresses the spring, thereby storing energy for actuation, and (2) lowers the capillary tube by a precise distance, to draw up a metered dose into the pumping chamber. The volume of the dose is 11–15 μL, depending on the drug. A non-return valve prevents the drug from returning to the cartridge. The patient then inhales slowly from the mouthpiece and pushes the dose-release button, which unleashes the tension in the spring and forces the drug through a nozzle system called a "uniblock."

The uniblock (Fig. 3) measures approximately 2 × 2.5 mm and consists of a silicone wafer sandwiched to a glass plate. A photolithographic technique is used to etch filter channels into the silicone. Two small, opposing channels at a carefully controlled angle form the exit of the uniblock, such that the 2 converging jets of liquid impact and form a soft mist (see Fig. 3b).

So far, the drugs studied with the Respimat have been those commonly used for asthma and COPD. The bronchodilators fenoterol and ipratropium bromide are aqueous drug solutions contained in multi-dose cartridges. The corticosteroid flunisolide is dissolved in 96% ethanol. The fine particle fraction produced by the latest version of Respimat is about 66% with the aqueous solutions and 81% with the ethanol solutions, which is higher than that of corresponding CFC pMDIs.[6]

The aerosol velocity from the Respimat is about one fifth of that from a CFC pMDI. The duration of aerosol generation is about 1.2 seconds for aqueous solutions and 1.6 seconds for ethanol solutions.[7] Though the Respimat requires synchronization of inspiration with actuation, the low velocity of the aerosol allows even poorly coordinated patients to capture the aerosol with a slow, deep inspiration.

### Respimat Deposition Studies

Gamma scintigraphy is a method for assessing lung deposition of inhaled drugs. Scintigraphic studies have been carried out for the Respimat with fenoterol (a $\beta_2$ agonist, not available in the United States) and flunisolide.[8] These studies were done with healthy volunteers and compared Respimat to a pMDI with and without a holding chamber. A randomized, 3-way crossover study was performed to compare fenoterol deposition with Respimat, pMDI, and pMDI with an Aerochamber.[9] Lung deposition values were 39.2 ± 12.7%, 11.0 ± 4.9%, and 9.9 ± 3.4% of the nominal dose, respectively. The Respimat showed less oropharyngeal deposition than the pMDI (37.1 vs 71.7%), but the pMDI plus AeroChamber had the lowest oropharyngeal deposition (3.6%).

Deposition of flunisolide was compared with the Respimat and a pMDI with an Inhacort spacer.[9] Lung deposition was 44.6 ± 7.9% with Respimat and 26.4 ± 6.2% with the pMDI plus spacer. Oropharyngeal deposition was 26.2% and 31.2%, respectively. In a prior study, with a pMDI without a spacer, the flunisolide lung deposition was 15.3 ± 5.1%, with oropharyngeal deposition of 66.9%.[10] Thus the Respimat reduced oropharyngeal deposition, eliminated the need for a spacer device, and increased lung deposition, compared with either MDI or pMDI with holding chamber.

### Respimat Clinical Studies

Though they can be used to compare device performance, in vitro and deposition studies are not enough to prove that one device/drug combination is superior to another in the clinical setting. Therefore, several clinical trials with asthma and COPD patients were performed to compare the Respimat to a CFC pMDI.[11] The studies using bronchodilators had the premise that lower doses with the Respimat would be equivalent to higher doses with the pMDI. VanNoord et al[12] studied 62 stable adult asthmatics, using a single dose of fenoterol from either the Respimat (range 12.5–200 μg per dose) or CFC pMDI (100 or 200 μg per dose). The forced expiratory volume in the first second ($FEV_1$) response was measured over a 6-hour period. This dose-ranging study showed that the 12.5 and 25 μg doses with the Respimat were therapeutically equivalent to the 100 μg dose with the pMDI. All Respimat doses were therapeutically equivalent to the 200 μg dose. A similar study by Goldberg et al[13] examined the bronchodilator response with a single dose of a formulation containing fenoterol and ipratropium bromide. That study showed that the Respimat had a log-linear dose-response relationship, as in the vanNoord study. It also showed that the bronchodilators administered with the Respimat were

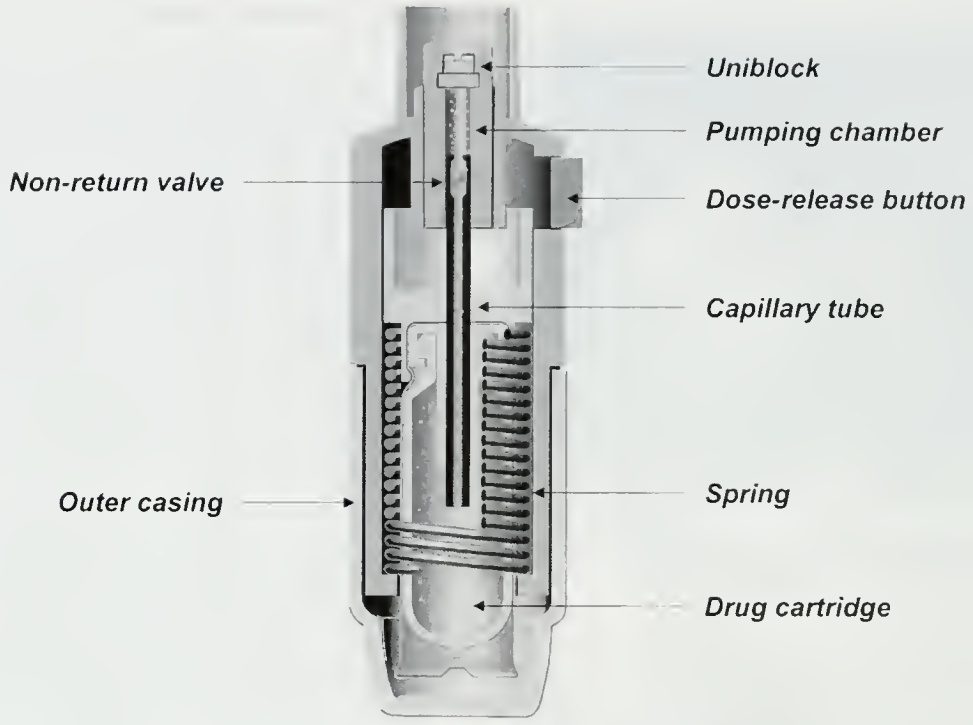


Fig. 2. Components of the Respimat. (Courtesy of Boehringer Ingelheim, Ingelheim am Rhein, Germany.)

therapeutically similar to the pMDI at one quarter to one eighth the dose. Pharmacokinetic analysis also showed a 2-fold greater systemic availability with the Respimat than with the pMDI. As in most studies, there was a high inter-subject variability in $FEV_1$ response. The safety profiles were similar between therapeutically equivalent doses.

Other studies with the combination of fenoterol and ipratropium bromide via the Respimat with asthmatics using cumulative doses (simulating doses used during acute exacerbations) have shown similar results. A study of 43 adult asthma patients showed that cumulative doses from the Respimat produced therapeutic equivalence at half the dose of the pMDI.[14] There was no paradoxical bronchospasm with repeated doses in either device in that study. A pediatric study of 461 asthmatic children between the ages of 5 and 15 showed a similar relationship with single doses of drug.[15] Subjects were treated for 4 weeks with fenoterol and ipratropium bromide via the Respimat or pMDI plus Aerochamber. The $FEV_1$ response on the final study day showed that the Respimat was twice as effective as the pMDI with holding chamber.

Clinical trials have also been performed with COPD patients with either ipratropium bromide alone or in combination with fenoterol. In each case the findings were similar to those of the asthma studies; that is, the Respimat was as effective at half the dose of the pMDI. Safety profiles were also similar between devices.[16–18]

### Challenges for Respimat

The Respimat has solved many of the problems of pMDIs, DPIs, and nebulizers. It is small, portable, and does not require a power source. It produces a slow-moving cloud with a high proportion of fine particles, which reduces mouth and throat deposition and allows a higher proportion of the emitted dose to be delivered to the lungs. It is also propellant-free and thus does not contribute to ozone depletion or global warming.

However, the Respimat still requires a degree of hand/breath synchronization. The patient must be inhaling when the device is activated, though with the Respimat the "soft mist" is produced over a longer period of time than a pMDI, making it easier for the patient to capture the aerosol during inspiration. The Respimat will have competition from DPI and HFA pMDI preparations of the same or similar drug combinations. The budesonide Turbuhaler can deposit up to 35% of the nominal dose in the lung.[19] The newer HFA pMDI beclomethasone has been shown to deposit more than 50% of the initial dose in the lung.[2] The introduction of a new aerosol delivery technology in the United States may face stiff competition from devices that are already familiar to physicians and patients.

Perhaps the largest challenge for Respimat is that there has been growing concern regarding the use of preservatives in drug formulations. Multi-dose liquid formulations need preservatives, and Respimat is a multi-dose device.

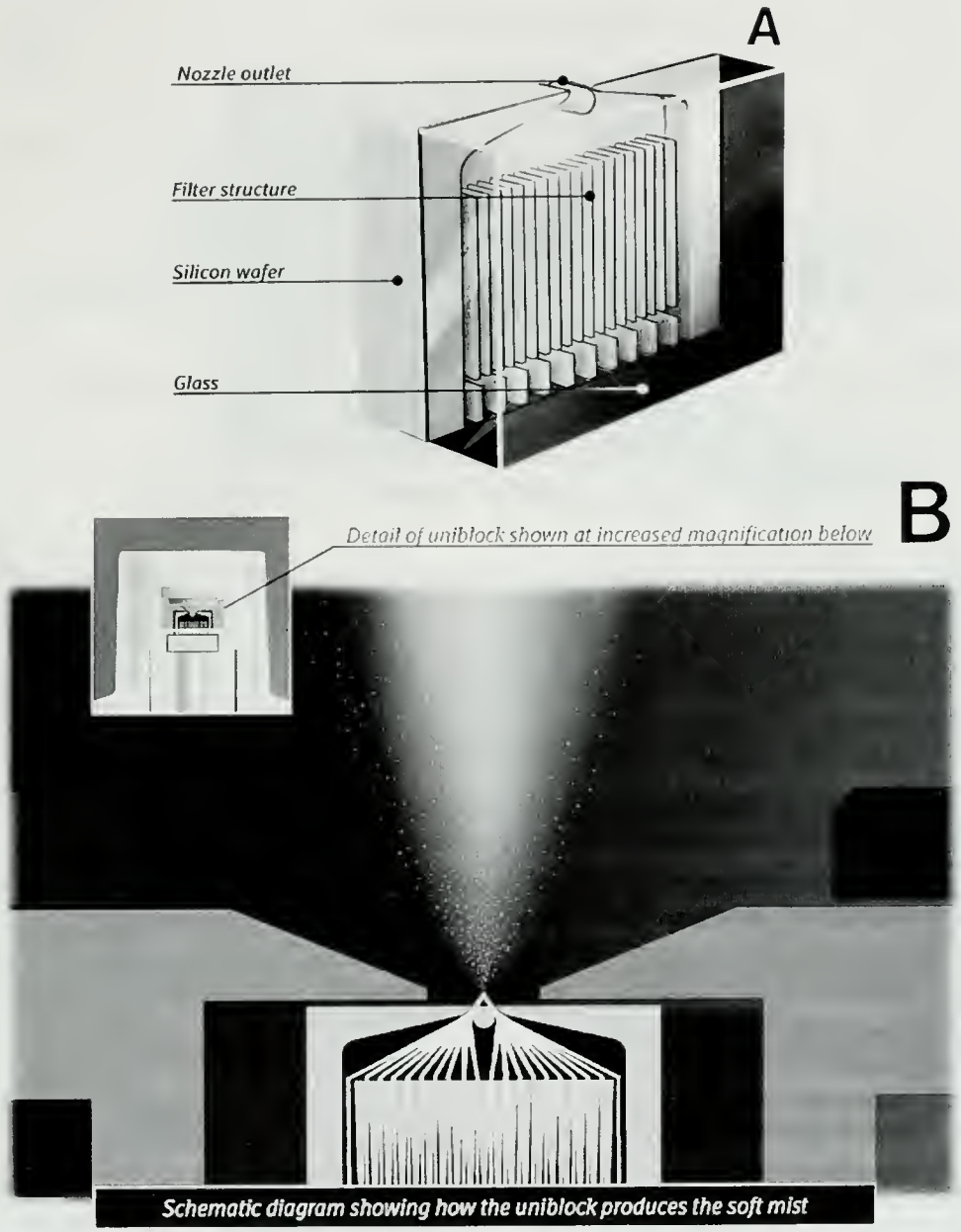


Fig. 3. A: Uniblock nozzle design. B: The 2 liquid jets exiting the uniblock nozzles converge to form a soft mist. (Courtesy of Boehringer Ingelheim, Ingelheim am Rhein, Germany.)

Aqueous Respimat solutions are preserved with benzalkonium chloride and ethylenediaminetetraacetic acid (EDTA), which have been implicated in causing paradoxical bronchoconstriction in asthmatics.[20] The inhalable steroid used in Respimat is preserved and stabilized with 96% ethanol, which has also been implicated in causing bronchospasm.[21] Even so, studies with the Respimat and asthmatic patients with substantial bronchial hyperactivity have shown it to be well tolerated.[22] The dose of benzalkonium chloride inhaled with several puffs of an aqueous Respimat solution is still considerably lower than that in some of the available nebulizer preparations in the United States. However, there has been increased interest in banning preservatives from inhaled drugs.[23] The current regulatory environment favors sterile, unit-dose drugs without preservatives, so the Respimat may face this hurdle in the United States.

### The AERx System

The AERx (Aradigm, Hayward, California) is an electronic microprocessor-controlled device designed to pro-

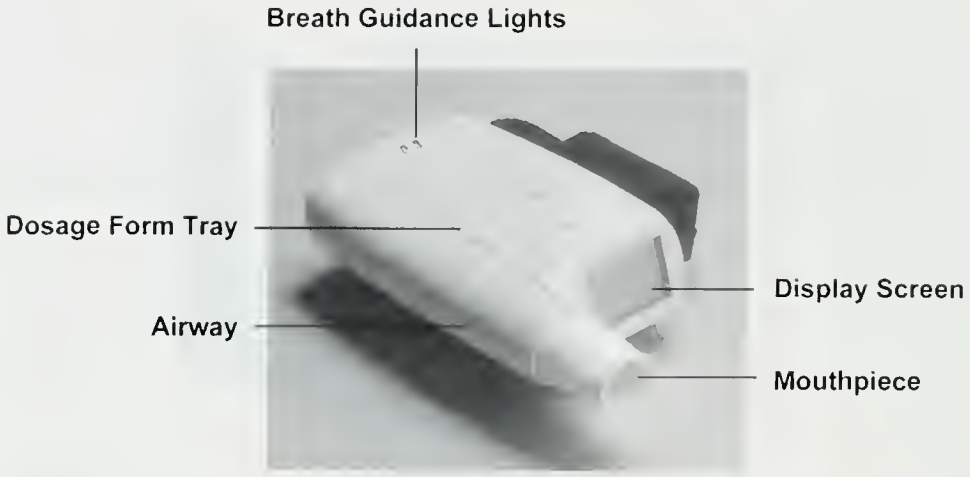


Fig. 4. The AERx system. (Courtesy of Aradigm, Hayward, California.)

Table 1. Therapeutic Agents Delivered by the AERx System

| Systemic Delivery | Topical Delivery |
|---|---|
| Proteins and peptides | Proteins and peptides |
| – Insulin | – rhDNase |
| – Interferon α2B | – IL-4 Receptor |
| Small molecules | Nucleotide |
| – Morphine, fentanyl | – INS365 |
| – Testosterone | Gene therapy vectors |

rhDNase = recombinant human deoxyribonuclease (dornase alfa).
IL = interleukin

vide precise dosing of liquid formulations to the lung, with a wide variety of therapeutic agents.[24] In order to achieve a high level of precision and drug targeting to the lung, the AERx controls all aspects of the dosing, including the generation of the aerosol and the patient's inhalation pattern. The AERx device (Fig. 4) is a hand-held, battery-powered, unit-dose system. The electronics function in several ways to improve dose precision and consistency, by (1) conditioning entrained air with a heating unit to reduce the influence of ambient conditions, (2) providing dose titration capability, (3) giving feedback to the patient for proper inhalation technique and breath-holding time, and (4) releasing a dose only if the patient's inhalation fits pre-set flow and volume targets. The AERx can also monitor dose times and frequency, download the information to the clinician, and provide safeguards against unauthorized use.

The AERx device was initially developed for noninvasive drug delivery for systemic diseases. However, the precision of the device has also proven effective for use with topical drugs to treat pulmonary diseases. Table 1 lists therapies that have been delivered with the AERx device, including peptides, proteins, hormones, and small molecules.

With the AERx the drug is contained in a single-use, multi-layer, laminated dose blister that consists of a drug reservoir and a burstable-seal layer with a slot that directs drug through a nozzle array (Figure 5A). The nozzle consists of a number of small laser-drilled holes approximately 1 $\mu$m in diameter. Since the nozzle array is incorporated in the dose blister, it is used only once, thus avoiding clogging issues, which improves the reproducibility and reliability of aerosol production. Each dose blister holds approximately 45 $\mu$L of liquid. In the case of higher dose requirements, the dose blisters can be manufactured in a strip so that after one dose is inhaled the next one is automatically loaded.

The AERx incorporates sophisticated technology to deliver aerosol during a pre-set portion of inspiration and only when conditions are ideal (Fig. 6). The dose blister is inserted into the strip guide, which advances it to the extrusion mechanism. The blister is held by a clamp that seals the perimeter to ensure a controlled release of drug. The blister is positioned above a piston mechanism driven by an electrical motor, which is capable of up to 50,000 actuations over the life of the device. A temperature controller heats the air to control temperature and relative humidity. This reduces the aerosol particle size variability that can be caused by ambient air conditions.

A pressure-sensing system located near the temperature controller measures the inspiratory flow and inhaled volume. The patient is guided to inhale at the desired flow rate by visual feedback from a display. When the AERx senses the proper flow rate, the motor/cam/piston assembly mechanically pressurizes the blister dose and extrudes the drug through the nozzle array. The aerosol produced is entrained in the inspired air (Fig. 7). The display screen then prompts the patient to hold the breath for a count of

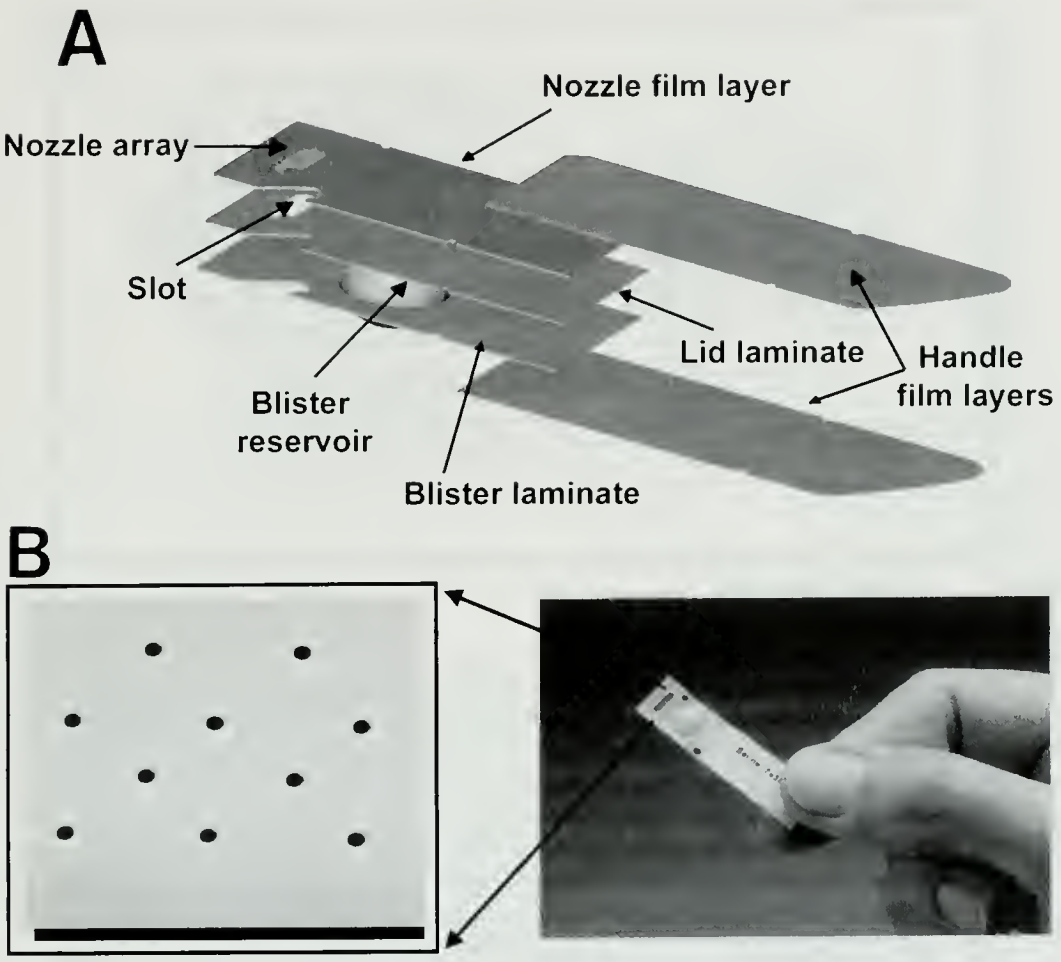


Fig. 5. A: The AERx dose blister is a multilayer laminate designed to force a liquid formulation through a nozzle. B: The nozzle is integral to the dose blister and consists of an array of 1-$\mu$m holes that produce a fine-particle mist. (Courtesy of Aradigm, Hayward, California.)

5–10 seconds. The dose is expressed over approximately 1.5 seconds. More than 90% of the particles are between 1 and 3 $\mu$m. The aerosol is nearly monodisperse, with a geometric standard deviation ranging from 1.2 to 1.5 $\mu$m, depending on the drug and device prototype. These characteristics of the AERx are ideal to achieve low oropharyngeal deposition and high peripheral lung deposition. The motor in the AERx also has a position-sensing system that allows increments of a dose blister to be administered. For example, the patient can set the AERx to deliver one-unit increments of insulin, allowing accurate dose titration by the patient. The nozzle array design and the timing of aerosol release can be changed to target the central lung regions for topical airway applications. By controlling the conditions of dose expression and managing the inhalation and delivery process, the AERx can provide the level of dose reproducibility that is required for a drug with a narrow therapeutic index.

### AERx Deposition Studies

Gamma scintigraphy studies with normal volunteers and asthmatics have shown deposition efficiency of 50–80% with various AERx prototypes. The electronics that monitor the patient inhalation profile prior to dosing are similar to those of an earlier device, the SmartMist, developed by Aradigm, which provided reproducible actuation of a pMDI at a pre-programmed point during inspiration.[25] A study with normal human subjects compared lung deposition with the SmartMist pMDI and the AERx.[26] The SmartMist's average deposition fraction was 21.7% (well above a typical CFC pMDI), and the AERx averaged 53.3%. The pMDI produced a high-velocity aerosol with throat deposition of 42%, versus only 6.9% with the AERx. In another study, a radiolabeled protein was delivered with the AERx device or a vented nebulizer (the PARI LC Star) to 4 asthma patients.[27] The AErx averaged 80% lung dose,

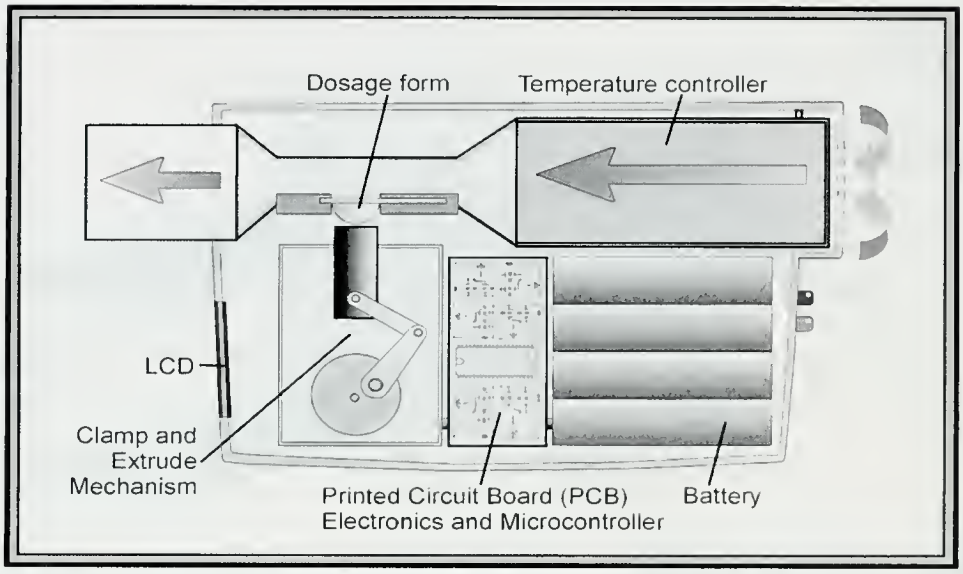


Fig. 6. Components of the AERx. (Courtesy of Aradigm, Hayward, California.)

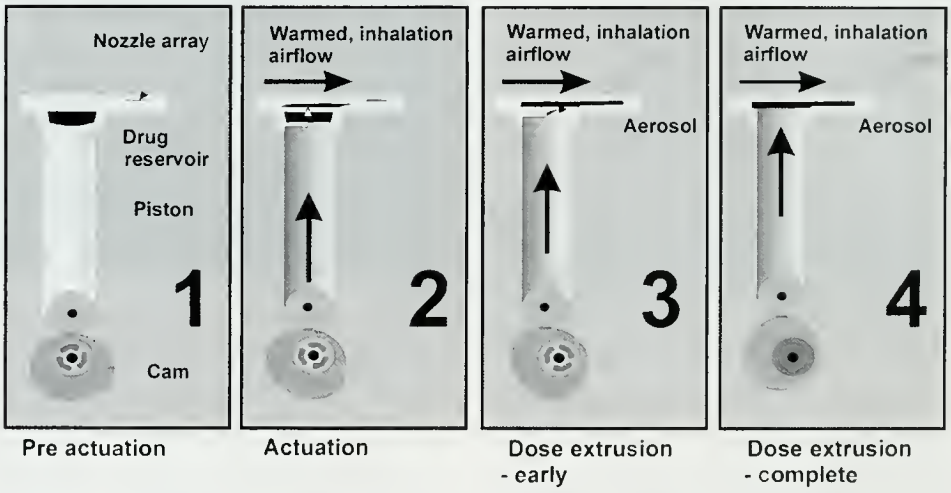


Fig. 7. Drug extrusion process with the AERx. (Courtesy of Aradigm, Hayward, California.)

compared to 33.6% with the PARI (Fig. 8). Even more impressive was the extremely low coefficient of variation with the AERx, which was only 3%, compared to 23% with the PARI. The reproducibility of lung delivery is far better with the AERx than with a pMDI, DPI, or nebulizer/compressor system.

### AERx Clinical Trials: Systemic Drugs

A number of therapeutic agents have been used or considered for use with the AERx, for either systemic or topical use. Traditional delivery routes for systemic agents include oral, transmucosal (rectal, buccal, nasal), transdermal, intravenous, intramuscular, and subcutaneous. Some drugs are broken down in the gut, and some molecules are too large to be absorbed efficiently through the skin or mucosa. The large, absorptive, alveolar-capillary surface of the peripheral lung provides an attractive alternative to other delivery methods for large or small molecules. The advantage of inhaling systemically active agents, versus intravenous, intramuscular, or subcutaneous administration, is the elimination of injections. The advantages of inhalation over oral or transmucosal delivery are faster onset of action, precise dose titration, and high bioavailability. The 2 indications for which the AERx has been most studied are pain control with inhaled opioids (morphine and fentanyl) and diabetes treatment with inhaled insulin. Pharmacokinetic, pharmacodynamic, efficacy, and

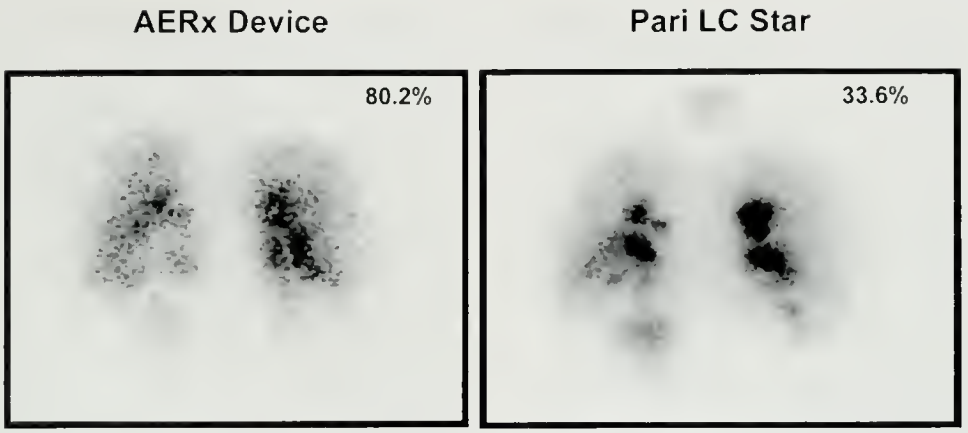


Fig. 8. Gamma camera images of interleukin (IL-4) receptor in an asthmatic show much greater lung deposition and more even distribution with the AERx than with the PARI LC Star nebulizer. (Courtesy of Aradigm, Hayward, California.).

safety studies have been performed with these drugs delivered by the AERx device.

Early studies of nebulized opioid inhalation for dyspnea had mixed results, but there was good evidence of analgesia, as reviewed by Otulana and Thippawong.[28] The level of pain control with inhaled opioids was directly related to the efficiency of the nebulizer system. Bioavailability is very low with traditional nebulizer systems, but the AERx can produce small particles in a controlled inhalation to maximize systemic absorption. Pharmacokinetic studies with morphine or fentanyl with the AERx device in healthy volunteers have shown systemic bioavailability ranging from 59 to 95%.[29–32] In one of these studies[30] the in vitro measurements showed that the AERx had an emitted dose of 78% and a mass median aerodynamic diameter ± geometric standard deviation of 2.6 ± 1.3 μm. The 10 subjects in that study had a mean bioavailability of 75%, showing close agreement with the in vitro data. The pharmacokinetic profile of inhaled opioids with the AERx was similar to intravenous administration in each of these studies, with rapid peak serum levels and a short half-life (Fig. 9).

To date, over 120 patients have been treated with inhaled opioids with the AERx Pain Management System. Boyle et al used the AERx system to deliver fentanyl to patients with pain from advanced cancer, and showed good analgesia in all patients, with average pain control within 10 min of administration.[33] A recent Phase 2 study with morphine showed greater and faster analgesia than immediate-release oral morphine in patients with breakthrough cancer pain.[34] Two other studies of morphine delivered by the AERx to patients with orthopedic postoperative pain showed pain relief and onset of action comparable to intravenous morphine.[35,36] The AERx Pain Management System's safety features include patient identification keys and physician-set lockouts to prevent unauthorized access. These studies demonstrate the potential to control acute and breakthrough pain with opioid inhalation from a precise dosing system such AERx.

Diabetes affects 150 million people worldwide. It has been demonstrated that tighter control of blood glucose levels in both type 1 and type 2 diabetes results in better long-term outcomes.[37,38] However, better glycemia control means more insulin injections per day, which may be an inconvenience or burden to some patients. Therefore insulin inhalation has been investigated with new aerosol devices, including AERx.[39] Data from healthy volunteers show faster insulin absorption via inhalation than via the subcutaneous route, but more insulin is required to achieve the same effect.[40] Insulin is a large molecule, and not all the insulin deposited in the lung is absorbed. But inhaling deeply rather than with a shallow breath results in much faster absorption of insulin, perhaps because of better peripheral lung deposition.[41] Kipnes et al reported insulin pharmacokinetic and pharmacodynamic responses after a standard meal in type 1 diabetics.[42] The mean system efficiency relative to subcutaneous dosing was 16–17%, which is comparable to or better than other new aerosol systems. The time to peak insulin level was 41 min shorter than with subcutaneous administration. Thus, dosing just prior to a meal is possible with the AERx, whereas a subcutaneous dose must be given 30–40 min before a meal.

Another study of type 1 diabetics showed a clear dose-response curve with the AERx system, and intra-subject variability similar to subcutaneous insulin administration,[43] demonstrating the reliability and precision of dosing with the AERx. Finally, a recent 12-week study of 107 people with type 2 diabetes showed equivalent responses with short-acting insulin delivered thrice daily with meals either via inhalation with the AERx system or via the subcutaneous route.[44] As with all the clinical trials with inhaled insulin, patients still required a nighttime subcutaneous dose of long-acting insulin. Therefore, the use of inhaled insulin with meals

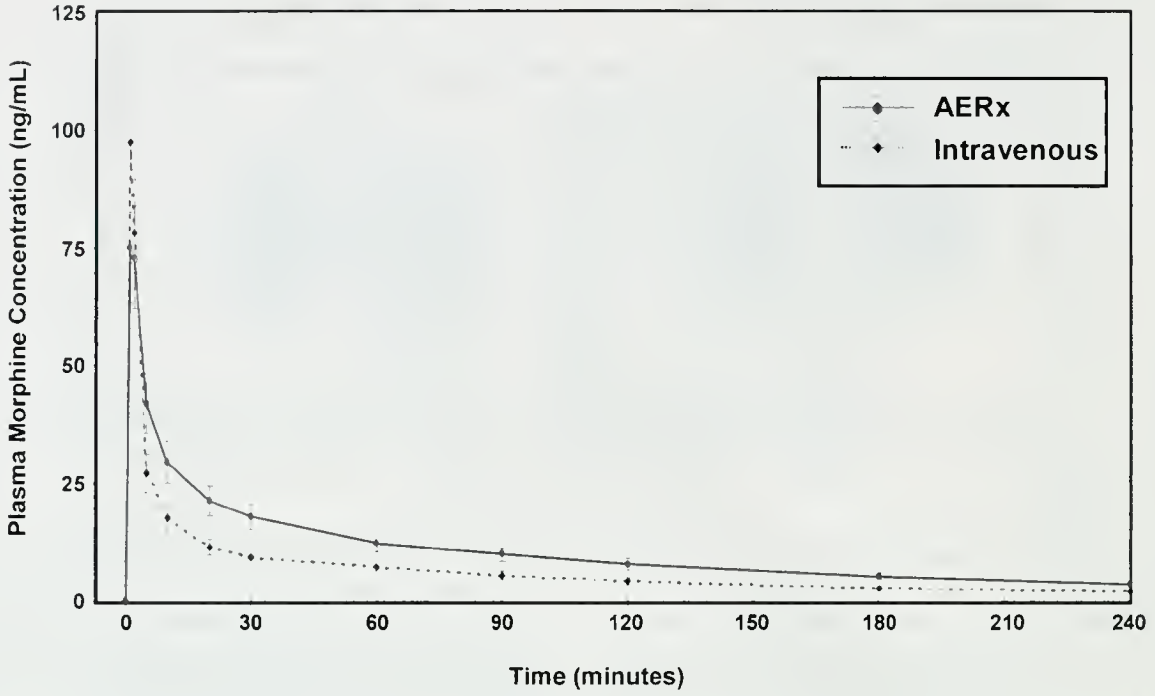


Fig. 9. Pharmacokinetic profile of morphine delivered via AERx is similar to intravenous administration. (From Reference 28, with permission.).

can result in tight glycemia control while reducing the number of injections to one per day.

### AERx Clinical Trials: Pulmonary Delivery for Lung Disease

Most inexpensive asthma drugs with a wide therapeutic index may not require the dose precision and efficiency of the AERx. However, there are a number of expensive drugs available and in development that could be delivered topically with the AERx to treat lung disorders. Efficient and rapid aerosol delivery systems are needed for chronic disorders such as CF that require daily therapy with numerous inhaled drugs. And there will be more such drugs in the future.

One expensive biotechnology product used for CF is rhDNase (dornase alfa or Pulmozyme), which reduces sputum stickiness and thus aids in sputum clearance. Using a standard, approved nebulizer may take 10–15 min (per 2.5 mg dose) and deposit only 6–31% of the dose in the lung.[45] A proof-of-concept study with the AERx and 16 CF patients with moderately severe lung disease showed that $FEV_1$ improvement averaged 9.9% after 2 weeks of daily bolus inhalation of rhDNase (1.35 mg in only 3 breaths).[46] That was the first report of bolus inhalation of a protein used for topical airway application.

Another drug with potential for CF, chronic bronchitis, and COPD is INS-365, which is a uridine triphosphate analogue that binds the P2Y2 receptor in airway cells. Activation of the receptor triggers chloride secretion and increases ciliary beat frequency, which promotes airway clearance. It is thought that a high lung dose (about 10 mg) of INS-365 is necessary to be effective, making it a challenging drug to administer by bolus technique. The AERx dose blister can only hold 50 $\mu$L of fluid, which would necessitate a high concentration of drug in the blister. Fortunately, INS-365 is highly soluble. Though the viscosity is greater at higher concentrations, the AERx was able to deliver more than 10 mg INS-365 (240 mg/mL) in only 2 inhalations.[47] Currently rhDNase and INS-365 are not being commercially developed for the AERx, but the latter studies demonstrate that the AERx can efficiently deliver such drugs to the airways.

### Challenges for the AERx System

The AERx measures the inhaled flow briefly before aerosolizing a dose over about 1.5 seconds. Thus, to inhale a full dose from the blister a patient must have a minimum vital capacity of 1.5 L. This prohibits the use of the AERx with young children or older patients with restrictive or severe obstructive lung disease, so modifications will be necessary before those populations can benefit from the AERx.

Some drugs, such as anti-proteases and aminoglycosides, require a large lung dose to be effective. Since the

AERx dose form only holds 50 μL, it is not a viable option for some drugs that are not stable at high concentrations.

Opioids delivered with the AERx provide pain relief similar to intravenous administration, with faster onset of action than oral or transmucosal administration. However, it is likely that the expense of the AERx Pain Management System will substantially exceed that of the other administration routes. Even if AERx is approved for morphine and fentanyl delivery, there is no guarantee that it will be reimbursed by third-party payors. The AERx also faces competition in the diabetes arena. Insulin pumps already provide strict glycemia control without multiple injections. A number of other insulin delivery systems are in development, including DPIs and liquid aerosol systems for inhalation, oral ingestion, and transmucosal methods. Regulatory concerns about the safety of inhaled insulin may delay approval long enough for other technologies to "catch up," including islet cell transplantation, which may eliminate the need for insulin. This could be financially devastating for the companies investing considerable resources in inhalable insulin research. Nevertheless, there will be many inhalable therapeutics for both topical and systemic delivery that will require the efficiency and precision of devices such as AERx.

## Summary

Aerosol delivery technology was stagnant until the past decade or so, when several forces ignited the fires of innovation in the industry. In the coming years we are likely to see several new drug/device products that will improve aerosol delivery efficiency and be much more user-friendly. The Respimat solves many of the problems with DPIs and pMDIs, by producing small particles in a slow-moving cloud. Because of its superior efficiency, Respimat can deliver asthma and COPD drugs at lower nominal doses while maintaining efficacy and safety. The AERx system can deliver a wide variety of liquid formulations for topical airway or systemic delivery. The dose accuracy and reproducibility of the AERx allow inhalation delivery of drugs that have narrow therapeutic windows. Both AERx and Respimat face regulatory, financial, and competition obstacles, but both technologies hold considerable promise to improve the lives of patients.

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## Discussion

**Gomez:** Since the AERx technique relies on forcing liquid through a 1-$\mu$m orifice, aren't there issues of clogging? That may be one of the reasons the lung deposition is not as good as some of the other techniques that also yield monodisperse aerosol. You can achieve higher lung deposition if you have relatively narrow droplet size distributions. In principle the distribution should be very narrow with this device, but perhaps it isn't because the droplets have to be generated through 1-$\mu$m orifices.

**Geller:** As I mentioned, the AERx does produce a fairly monodisperse aerosol. It's a much smaller (GSP) distribution than a nebulizer, for example, though it's probably not as monodisperse as the electrospray technology. But the AERx holes are laser drilled and they're uniform in size. It's a disposable, inexpensive blister. The nozzle array is just holes drilled into a film material, and they *do* get clogged after one use. I've seen a micrograph of a clogged nozzle. If you have to take 3 doses (that

is, 3 dose blisters), they make a little cassette that automatically ejects the used one and loads the next. It's not 100% deposition, but somewhere between 50 and 80% lung deposition of the nominal dose is great—a lot better than nebulizers.

**Dennis:** The design of the AERx device has taught me something very valuable. Aradigm put a lot of investment into their device, to control the temperature and the humidity of ambient air, and to ask the patient to inhale at a certain rate. I've talked with Igor Gonda [Aradigm research and development] about this, and I believe it's true that the reason Aradigm did that is that they want to control the amount of evaporation in the aerosol bolus. The AERx has a 50 $\mu$L bolus that emits in 1 second into an air stream in which temperature and humidity are controlled. The Respimat only has a 15 $\mu$L bolus that emits in 1 second into roughly the same ambient air flow rate, but with no temperature or humidity control. So the Respimat cannot avoid a lot of variable aerosol evaporation and the resulting decrease in droplet size, which is dependent on the amount, humidity, and temperature of inhaled air.

To my knowledge, Boehringer has not addressed that at all. I haven't seen anything in publication or during conference discussion. Even so, the device will undergo clinical trial, so this should prove its safety and efficacy for a specific application, though the variable evaporation will be important for generic application. There's a message here to *anybody* who's developing devices that emit a small bolus of liquid aerosol, which is that the amount of evaporation to ambient air will be as much as about 16–18 $\mu$L/L in dry air, so, with 50% humidity, evaporation will be about 8 $\mu$L of water from the aerosol droplets. If you have a small bolus volume of only 10–20 $\mu$L from a device releasing into a liter of air, that evaporation is going to *seriously* affect the particle size, and you'll probably end up with either dry particles or very much concentrated particles.

**Geller:** I do have one comment. I forgot to mention that Aradigm (AERx) is developing a completely *mechanical* device as well. The electronics, obviously, are expensive, and there are some drugs that do not require the precision of the electronic version, so they are developing a mechanical device. I don't know a lot about it, but it does *not* have a temperature controller, and I did see mention of one study that looked at temperature control versus no temperature control, and there was only a 5% difference in deposition.[1] So the temperature control *did* help, but only by 5%.

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**Fink:**[*] Was there a difference in particle size?

**Geller:** It didn't say.

**Fink:** The Respimat is a really cool device. We've been reading about it for years. Has it been released in Europe? Is there a plan to release it in the United States? What are the barriers?

**Geller:** Right now, neither AERx nor Respimat is available anywhere. I'm told that Respimat will go for application in Europe next year. There are some things in development that I'm probably not supposed to know about, so I can't say. And I believe there *is* a move to market in the United States as well. I think the barrier is going to be the drug preservatives the device requires.

**Witek:**[*] A couple of points about the Respimat Soft Mist Inhaler. It is being developed as an alternative to common metered-dose inhalers and dry powder inhalers. It is a pocket-sized, multi-dose device for the delivery of bronchodilators and other agents for COPD and asthma. With regard to the timelines, you're right about the application in Europe, and the Phase III studies will be starting in the United States this year. Regarding your point about preservatives. . . I guess these are the balances we have. As Paracelsus said: It's all in the dose. Respimat uses very low doses of preservative, and it will be seen in the clinical trials if the preservative is a problem. We've done some small-scale studies in which it appeared *not* to be, even in hypersensitive individuals.[1–3]

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* James B Fink MSc RRT FAARC, Aerogen, Mountain View, California.

* Theodore J Witek Jr DrPH RRT FAARC, Boehringer Ingelheim, Ingelheim am Rhein, Germany.

# Nebulizers That Use a Vibrating Mesh or Plate with Multiple Apertures to Generate Aerosol

Rajiv Dhand MD

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Summary

**Several electronic nebulizer devices that use a vibrating mesh or plate with multiple apertures to generate a fine-particle, low-velocity aerosol have been marketed or will shortly become available for clinical use. These devices have a high efficiency of delivering aerosol to the lung, such that the nominal dose of drugs to be administered could be substantially reduced. Moreover, the volume of drug solution left in these new devices when the nebulization has ceased is negligible, so there is potential to improve the cost-effectiveness of administering expensive medications. Because these devices nebulize at a faster rate than conventional jet or ultrasonic nebulizers, the duration of each treatment could be shortened. These devices efficiently nebulize solutions and suspensions; they have been successfully used for aerosolizing insulin, other proteins and peptides, and fragments of DNA. They could be employed for a wide variety of clinical applications, including the delivery of aerosols for systemic therapy and gene transfer. These devices have overcome many of the limitations associated with conventional jet and ultrasonic nebulizers, and they offer the versatility to modify the aerosol characteristics according to the clinical application for which they are employed. With these devices clinicians will be able to precisely control drug delivery to the respiratory tract.** *Key words: nebulization, nebulizer, aerosol, vibrating mesh, vibrating plate.* [Respir Care 2002;47(12):1406–1416]

## Introduction

Nebulizers convert liquids into aerosol particles for deposition in the lower respiratory tract.[1,2] A pneumatic (jet) nebulizer uses the energy provided by compressed gas flow to generate an aerosol, whereas an ultrasonic nebulizer uses electricity to vibrate a piezoelectric crystal at high frequency. Standing waves are generated when the high-frequency vibrations are focused onto the surface of the medication solution. Liquid droplets break off from the wave crest to form an aerosol.

For several decades nebulizers have been employed to deliver medications via inhalation. Indications for aerosol therapy, however, are rapidly expanding. In the not-so-distant future, aerosols could be used to deliver drugs to the respiratory tract for systemic effects[3] and to deliver genes to the respiratory tract.[4] There is a need for better technology to improve the *efficiency*, *precision*, and *consistency* of aerosol deposition in the lung, to use new formulations, and to allow efficient aerosolization of suspensions and drugs with high lipid solubility.[4,5] In addition, there needs to be a concerted effort to protect respiratory therapists and other health care workers from occupational exposure to aerosolized drugs.[6]

This review discusses several new devices that have in common the ability to aerosolize a drug solution by using a vibrating mesh or plate with multiple apertures. These devices offer important advances in our ability to deliver aerosolized drugs to the respiratory tract.

## Design Features of Aerosol Generators That Use a Vibrating Mesh or Plate with Multiple Apertures to Generate Aerosol

Several manufacturers (Aerogen, Mountain View, California; Omron, Vernon Hills, Illinois; and ODEM, Royston, Hertfordshire, United Kingdom) have developed the technology that uses a vibrating mesh or plate with multiple apertures to produce a liquid aerosol. Table 1 lists the devices that have been developed or are under development.

Rajiv Dhand MD is affiliated with the Division of Pulmonary, Critical Care, and Environmental Medicine, University of Missouri-Columbia, Columbia, Missouri.

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Correspondence: Rajiv Dhand MD, Division of Pulmonary, Critical Care and Environmental Medicine, University of Missouri-Columbia, One Hospital Drive, DC043.00, Columbia MO 65212. E-mail: dhandr@health.missouri.edu.

Table 1. Aerosol Devices That Use a Vibrating Mesh or Plate with Multiple Apertures

| |
|---|
| *Aerogen - Aerosol Generator* |
| – Aeroneb portable nebulizer system |
| – Aeroneb professional nebulizer system |
| – Aerodose inhaler |
| – Aerodose insulin inhaler |
| *Omron - Vibrating Mesh* |
| – NE-U03 |
| – NE-U22 |
| *ODEM - TouchSpray Technology* |
| – TouchSpray inhaler devices |
| *PARI* |
| – eFlow |

Some features are common to all the devices that use a vibrating mesh or plate with multiple apertures to generate aerosol. These devices generate aerosols with a high fine particle fraction,[7] and they have a significantly higher efficiency of delivering drugs to the respiratory tract than do conventional jet or ultrasonic nebulizers. The aerosol is generated as a fine mist and no baffling system is required in these devices. Other features of these devices are that they are portable, battery-operated (operation with alternating current is optional in some devices), and they efficiently aerosolize solutions and suspensions with minimal dead volume (volume of liquid remaining in the nebulizer at the end of nebulization). Some of these devices are breath-actuated, thereby limiting the amount of aerosol released into the ambient air.

### Aerogen's Aerosol Generator

Aerogen's aerosol generator consists of a vibrational element and a domed aperture plate. The ceramic vibrational element expands and contracts when electrical current is applied to it. This contraction and expansion produces an upward and downward movement in the domed aperture plate (Fig. 1). The aperture plate has up to 1,000 tapered holes, which are electroformed in a sheet. The wider portion of the hole is toward the medication, and the narrower end is toward the atmosphere. The medication is placed in a reservoir above the domed aperture plate. During operation, upward and downward movement (by a few microns) of the aperture plate creates a micro-pumping action that extrudes the medication through the holes to produce an aerosol. Particle size, flow, and fine particle fraction are functions of the aperture hole exit diameter. The size of the holes in the aperture plate and, in turn, the size of the aerosol particles can be modified for specific clinical applications.

The devices that incorporate the Aerogen aerosol generator (Fig. 2) can be battery-operated, so they are porta-

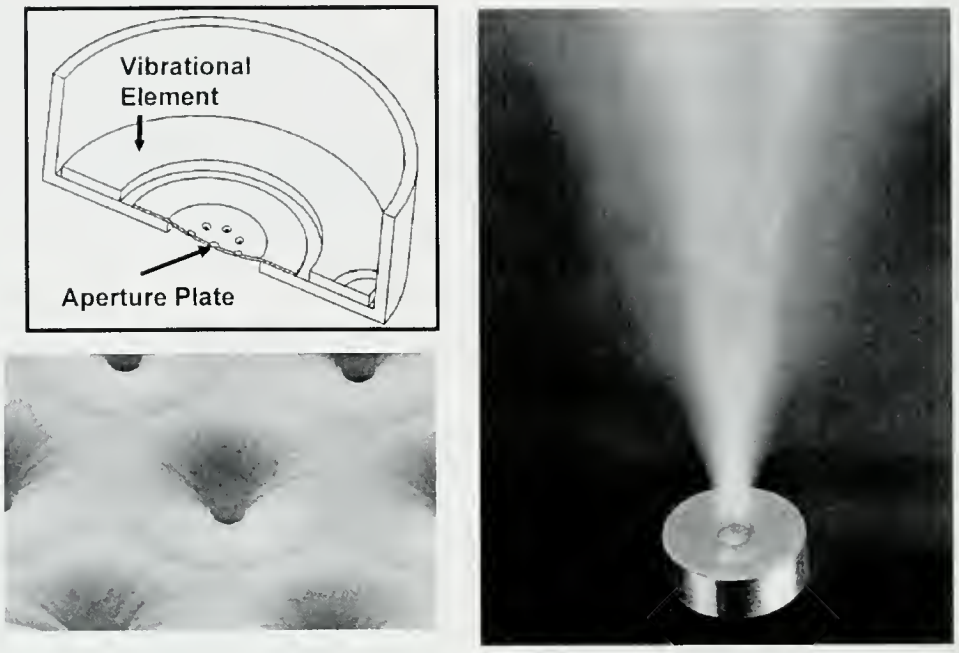


Fig. 1. Components of Aerogen's aerosol generator. Top Left: When the vibrational element is made to contract and expand by application of electrical current the up-and-down movement (by a few microns) of the aperture plate creates a micro-pumping action that extrudes the liquid through the apertures. Bottom Left: Microscopic view of apertures. There are approximately 1,000 apertures on the aperture plate. Right: A low-velocity mist is generated. (Courtesy of Aerogen, Mountain View, California.)

ble. These devices nebulize at 0.3–0.6 mL/min, generally requiring less time for drug delivery than conventional nebulizers. Because they do not require any compressed gas flow or high-energy vibration, their operation is relatively quiet. Another important advantage is that the dead volume is minimal. In fact, the aerosol generator can aerosolize almost down to the very last drop of liquid, whereas the dead volume in conventional jet or ultrasonic nebulizers is 0.3–1 mL. Some of Aerogen's devices are designed to operate in any orientation, including inverted. Aerogen's aerosol generator efficiently nebulizes suspensions, proteins, and peptides. Because the energy required for nebulization is applied to the vibrational element in the aerosol generator rather than to the fluid, temperature increase in the fluid is minimized, which minimizes the risk of denaturing proteins or peptides or reducing the activity of antibiotics.

### Omron's Vibrating Mesh Technology

The Omron technology incorporates a piezoelectric crystal that vibrates at a high-frequency when electrical current is applied. The vibration of the crystal is transmitted to a transducer horn that is in contact with the liquid to be aerosolized (Figs. 3–5). Vibration of the transducer horn causes upward and downward movement of the mesh plate, and the liquid passes through the apertures in the plate to form an aerosol. The mesh plate consists of numerous (up to 6,000) tapered holes, each approximately 3 $\mu$m in diameter. These holes amplify the vibration of the transducer horn throughout the medication and reduce the amount of power required to generate the aerosol. Using a low frequency of vibration with a mesh plate containing numerous minute holes allows efficient generation of a fine-particle mist.

The Omron devices are battery-operated and alternating-current-powered, produce a low-velocity aerosol, and require no propellant or compressor. They are portable and can produce an aerosol in almost any orientation.

### ODEM's TouchSpray Technology

ODEM's TouchSpray technology employs a perforate membrane that vibrates at high frequency against a body of liquid. The vibration source is a piezoelectric actuator, which is activated by a simple electronic drive circuit. The perforate membrane is a wafer-thin plate of stainless steel with many laser-drilled holes. The actuator and the perforate membrane form the TouchSpray atomization head, which is in contact with the liquid to be aerosolized (Fig. 6). Liquid jets are created as an inertial response to the vibration of the perforate membrane. Surface tension and hydrodynamic effects then cause these jets to break up to produce streams of precisely controlled droplets. This stream has a low velocity, and the atomization head can generate an aerosol in any orientation.

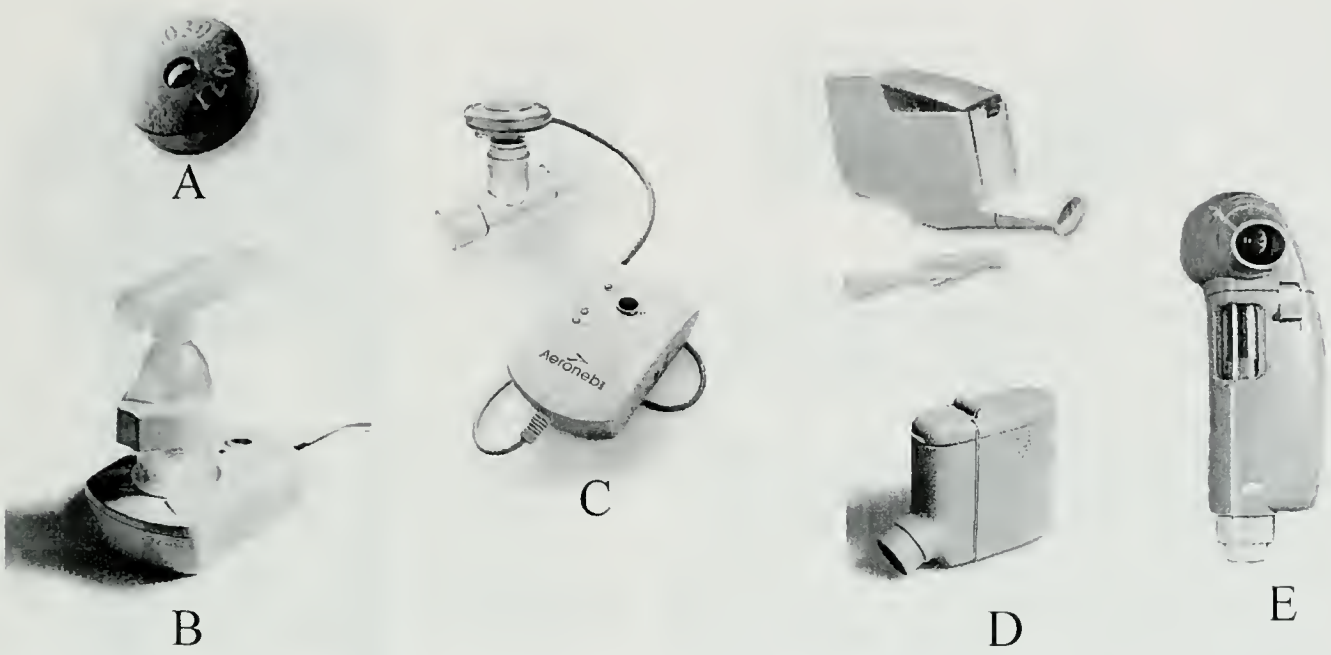


Fig. 2. Aerogen's aerosol generator and devices that incorporate it. A: Aerosol generator. B: The Aeroneb System is a hand-held device for home use. C: The Aeroneb Pro is an in-line device for delivering aerosols to mechanically-ventilated patients. D: The Aerodose Inhaler (2 versions) is a hand-held, battery-operated, breath-actuated device that incorporates individual nebules of commonly used bronchodilator solutions. E: The Aerogen Insulin Inhaler consists of an insulin pen and aerosolization head. The patient dials the insulin dose into the reservoir, and the protein is then quickly aerosolized with high efficiency and minimal dead volume. (Courtesy of Aerogen, Mountain View, California.)

The TouchSpray inhaler devices can efficiently aerosolize a wide range of liquids and particulate suspensions. With these devices the particle size and flow of the aerosol can be precisely controlled.

## Characteristics of Devices

### Aerogen Devices

**Aeroneb Portable Nebulizer System.** The Aeroneb Portable Nebulizer System is a simple, compact, silent nebulizer that delivers a fine-particle, low-velocity aerosol. The Aeroneb system is designed for use by ambulatory patients and for delivering nebulizer treatments in the hospital. Alternating current, alkaline batteries, or a car adapter can power the Aeroneb. This device does not require any propellants or a compressor system, and it can operate in a variety of orientations. Figure 2 shows a model of the Aeroneb.

**Aerodose Inhaler.** The Aerodose Inhaler is a small, hand-held inhaler that uses Aerogen's aerosol generator. This device is powered by 4 AAA batteries, does not require an external power source, and is breath-actuated. An inhalation sensor detects inspiratory flow above a threshold of approximately 10 L/min and synchronizes aerosol generation with inspiration. The sensor signals to terminate aerosolization when inspiratory flow falls below the threshold for actuation. Indicator lights on the device flash when the inhaler is turned on and is ready for operation. During inhalation the lights remain lit without flashing. Once the dose has been aerosolized, the indicator light shuts off. There is also a red light that indicates low batteries. When the batteries reach a very low level, the red light glows continuously, at which point the batteries need to be replaced immediately. Approximately 30 min of aerosol delivery time can be expected from a new set of batteries. A bypass button at the rear of the power supply can be used to trigger aerosolization to test the device or during cleaning.

The physical size and shape of the device is similar to that of a metered-dose inhaler (MDI). The velocity of the aerosol emitted from the Aerodose Inhaler is only about one tenth that of an MDI aerosol. The low-velocity aerosol produced by the Aerodose Inhaler is more easily entrained into the patient's inspired air than the high-velocity aerosol emitted from an MDI. The lower aerosol velocity reduces oropharyngeal deposition of drug particles. Single-dose nebules of standard bronchodilator solutions can be used with this device. It usually takes less than 2 or 3 minutes to deliver a bronchodilator treatment with the Aerodose Inhaler.

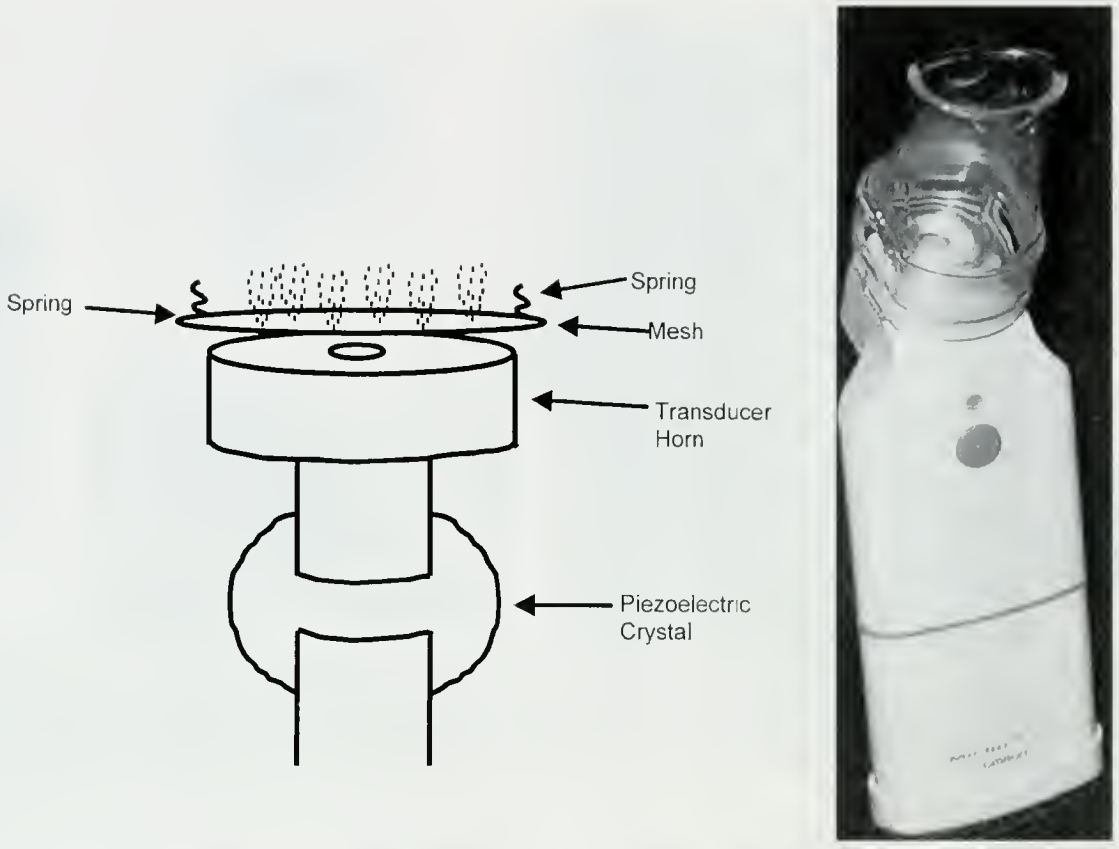


Fig. 3. Omron's NE-U03 nebulizer. Left: Principle of aerosol generation. The piezoelectric crystal is made to vibrate by application of electrical current from 4 AA batteries. This leads to vibration of a transducer horn placed in the reservoir of liquid to be aerosolized. Liquid passes up through the hollow center of the transducer horn. A ceramic plate above the transducer horn contains several hundred tapered holes. Springs attached to the plate control its vibration. A fine-particle mist is generated as the liquid passes through the apertures in the mesh plate and breaks up into small particles. Right: A model of the assembled device. (Courtesy of Omron, Vernon Hills, Illinois.)

**Aeroneb Professional Nebulizer System (Aeroneb Pro).** The Aeroneb Pro is a novel system designed for use during mechanical ventilation. The Aeroneb Pro is connected in the inspiratory limb of the ventilator circuit and generates aerosol continuously (see Fig. 2). It can be adapted to generate aerosol only during inspiration. The power for generating the aerosol comes from an alternating current outlet or from a rechargeable battery pack within the device.

**Aerodose Insulin Inhaler.** The Aerodose Insulin Inhaler is a small device, about the size of a cellular telephone. It has a rechargeable battery in a single unit that can fit into a pants pocket (see Fig. 2). It contains a cartridge of liquid insulin that contains approximately a 1-week supply. The patient dials in the pre-meal dose with an insulin pen-type mechanism that can provide 1-unit increments of insulin dose. The liquid insulin is rapidly aerosolized into small particles by the aerosol generator and inhaled into the lungs in a few breaths. The insulin deposits in the lung and is then absorbed into the bloodstream.

### Omron Devices

**NE-U03.** In the NE-U03 (see Fig. 3) the vibration of the piezoelectric crystal produces rapid movement of a transducer horn within the medication cup. The liquid medication passes through the hollow center of the transducer horn and through the mesh plate. The movement of the transducer causes vibration of the ceramic plate; springs attached to the ceramic plate prevent it from breaking. The liquid passes through the holes in the vibrating mesh plate to form an aerosol. The frequency of the current applied to the piezoelectric crystal is much lower than that employed in standard ultrasonic nebulizers, making electricity from a wall outlet unnecessary (but optional). The NE-U03 can operate for 5 hours on a set of 4 AA batteries. The energy is applied to the transducer horn rather than to the liquid medication, which minimizes the risk of denaturing the drug by heating during nebulizer operation. Similar to Aerogen's aerosol generator, the NE-U03 can nebulize solutions and suspensions almost down to the last drop of

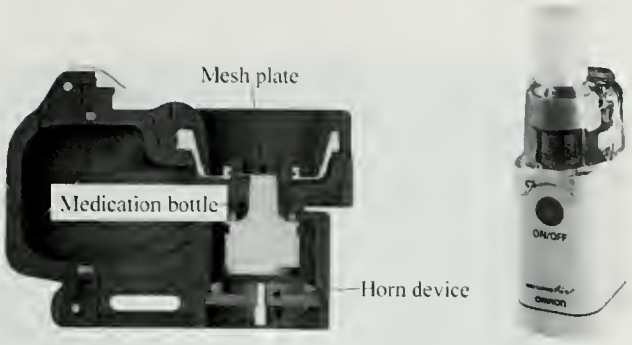


Fig. 4. Omron's NE-U22 nebulizer. A: Mechanism by which aerosol is generated. The liquid to be aerosolized is placed in the medication bottle, which is covered with a mesh plate containing several hundred electroplated apertures. Applied electrical current causes the piezoelectric crystal to vibrate, the vibration is transmitted to a transducer horn, and the transducer horn transmits the vibration to the liquid, which forces the liquid through the apertures in the mesh plate. B: A model of the assembled device. (Courtesy of Omron, Vernon Hills, Illinois.)

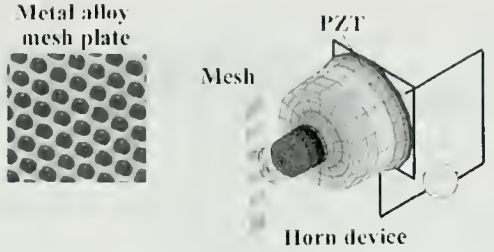


Fig. 5. Design aspects of Omron's NE-U22 nebulizer, optimized for nebulization of small volumes. Left: The mesh plate is made of metal alloy and the apertures are electroformed. The mesh plate is biocompatible, durable, and resistant to corrosion. Right: Arrangement of the piezoelectric crystal (PZT), transducer horn, and medication bottle. The transducer horn amplifies the vibration of the piezoelectric crystal and liquid from the medication bottle is pushed out through the mesh plate, which forms a fine-particle aerosol. This design offers low dead volume and higher amplified vibration with lower electric power. (Courtesy of Omron, Vernon Hills, Illinois.)

liquid, so that the dead volume is negligible. It is also position-independent in its operation.

**NE-U22.** Currently the NE-U22 (see Figs. 4 and 5) is marketed only in Japan. A medication bottle is connected to a transducer horn, and high-frequency vibration of the piezoelectric crystal is transmitted to the transducer horn. The vibration of the horn pushes the liquid medication through apertures in the mesh plate above it. Unlike the NE-U03, the NE-U22 has a metal alloy mesh plate in which the holes are produced by electroplating, thereby making the mesh plate more stable, biocompatible, durable, and resistant to corrosion. In contrast to the NE-U03, the metal end of the tapered holes in the NE-U22 is toward the medication, and the wider end is toward the atmosphere. The NE-U22 uses more energy than the NE-U03, but the frequency of vibration is considerably less than that employed in standard ultrasonic nebulizers. The NE-U22 also nebulizes down to the last drop, such that dead volume is negligible. The aerosolization head on the NE-U22 can be disconnected for cleaning.

In conventional nebulizers, diluents are added to the drug solution to increase the volume of solution to be aerosolized, because up to 1 mL of solution may remain in the nebulizer. Because the Omron NE-U03 and the NE-U22 can aerosolize with as little as 0.2 mL of solution, the need for diluent is eliminated.

### ODEM TouchSpray Inhaler Devices

The ODEM TouchSpray Inhaler devices are under development, in partnership with various pharmaceutical companies. These devices are small, simple to use, portable, have low power consumption, and they can be custom designed for various clinical applications. They are configured for single-dose or multi-dose drug delivery, and their high rate of aerosol flow allows treatments to be completed in a few breaths. Some of these devices will incorporate features such as breath-actuation and compliance monitoring. Figure 6 shows a concept model of a device incorporating ODEM's TouchSpray technology.

### PARI eFlow

The eFlow incorporates the TouchSpray atomization head (see Fig. 6). The eFlow is a small, portable, and silent device that is highly efficient for nebulizing solutions and suspensions. The nebulizer produces an aerosol with a high fine particle fraction and an output of up to 0.5 mL/min.[8] Aerosol is delivered continuously via tidal breathing. The eFlow is expected to be available for clinical use within the next year.

## Comparison of Vibrating Mesh/Plate Devices and Conventional Jet and Ultrasonic Nebulizers

### In Vitro Comparisons of Efficiency in Aerosolizing Solutions

Several investigators have compared the performance of vibrating mesh/plate aerosol devices and conventional jet and ultrasonic nebulizers.

Using an adult breathing pattern, the Aeroneb system was shown to aerosolize albuterol solution (0.083%) at a flow of 0.41 mL/min, compared to 0.20–0.36 mL/min with various jet nebulizers, such as the PARI LC Plus, DeVilbiss 800, Allegiance Air Life MistyNeb, and Salter

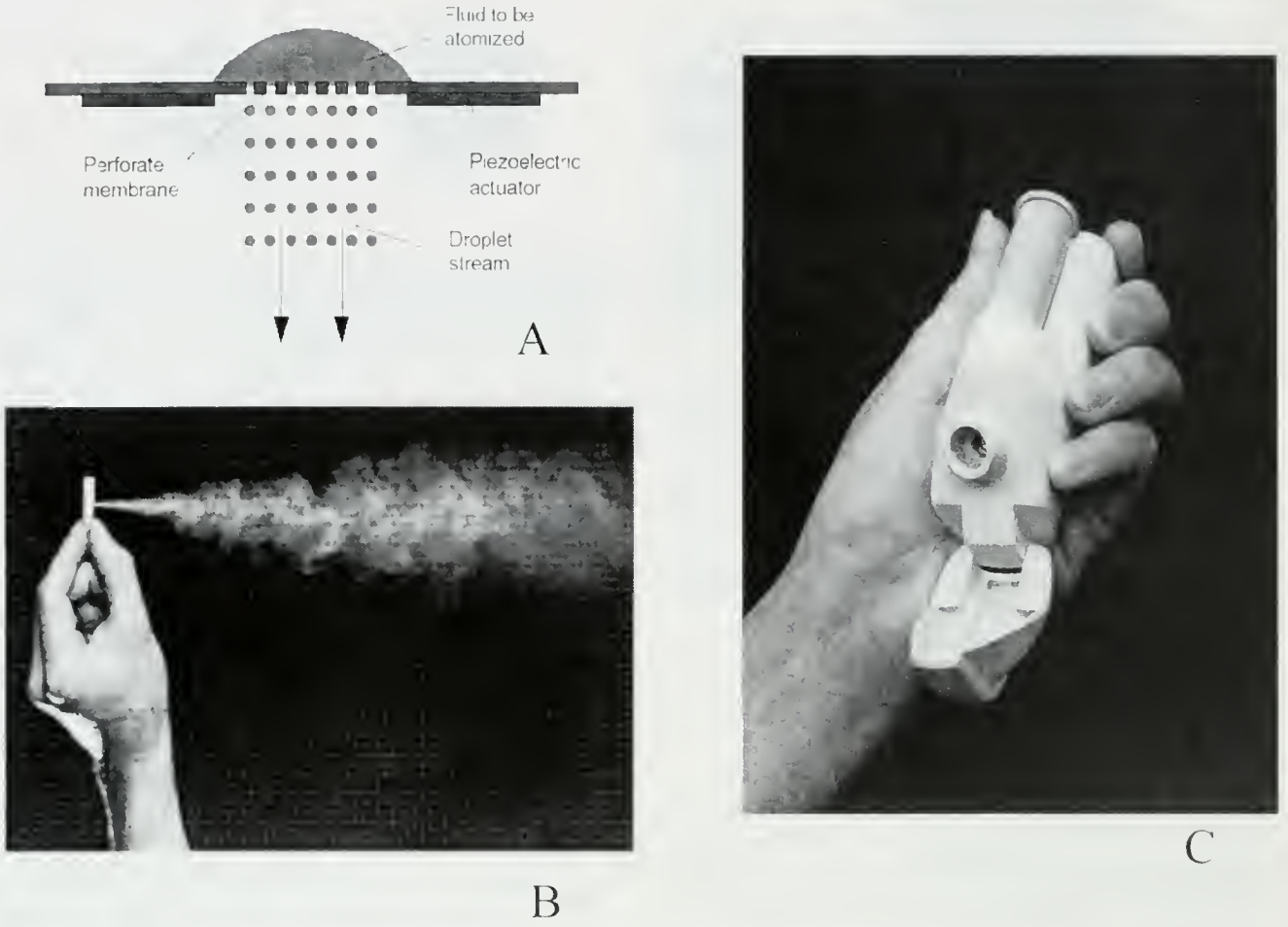


Fig. 6. A: TouchSpray atomizing head design employed in the ODEM inhaler and PARI eFlow. The liquid to be aerosolized is in contact with a perforate membrane. An electronic drive circuit is used to drive a piezoelectric actuator. The TouchSpray atomizing head contains the piezoelectric actuator and perforate membrane. Vibration of the perforate membrane against the liquid to be aerosolized forms small jets that emerge from the perforate membrane and form droplets of precisely controlled size and low velocity. B: Aerosol produced during operation. The dose is delivered continuously during tidal breathing. C: A concept model of an ODEM TouchSpray Inhaler. (Courtesy of ODEM, Royston, Hertfordshire, United Kingdom.)

Labs 8900.[9] With the Aeroneb system the volume median diameter (VMD) ranged from 4.1 to 5.9 $\mu$m, corresponding to a mass median aerodynamic diameter (MMAD) of 1.4–2.8 $\mu$m and a fine particle fraction of 60–70%. Those values compared favorably with the particle sizes generated by the conventional jet nebulizers.[9] The mass of albuterol in the fine particle fraction with the various nebulizers ranged from 0.1 to 0.34 mg, corresponding to 3.9–13.5% of the nominal dose. The fine particle fraction delivered with the Aeroneb System was comparable to that produced by the breath-enhanced PARI LC Plus nebulizer and was higher than that delivered by the DeVilbiss 800, Allegiance Air Life MistyNeb, and Salter Labs 8900.[9]

Fink et al compared the performance of the Aeroneb Pro and 2 small-volume jet nebulizers (MistyNeb and Vix-One).[10] The ability to deliver 2.5 mg of 0.083% albuterol sulfate solution was tested in a simulated pediatric patient receiving mechanical ventilation with high-frequency oscillation. The Aeroneb Pro delivered 3 times more albuterol to the distal end of the endotracheal tube than the conventional small-volume nebulizers. In contrast to the Aeroneb Pro, the gas flow used to operate the jet nebulizers required a change in ventilator variables, and refilling the jet nebulizers required interruption of ventilation.[10]

The Aeroneb Pro was compared with the Siemens Ultra Nebulizer 145 (SUN 145) in a model of adult mechanical ventilation.[11] The output from the SUN 145 was influenced by medication volume and by the air flow through the device (at 6, 30, and 60 L/min), with the highest output being observed at 60 L/min (Fig. 7). The output from the Aeroneb Pro remained stable at various medication volumes and air flow rates.[11] In contrast to the SUN 145, the Aeroneb Pro aerosolized the solution even in the inverted position (with the reservoir above the aerosol generator

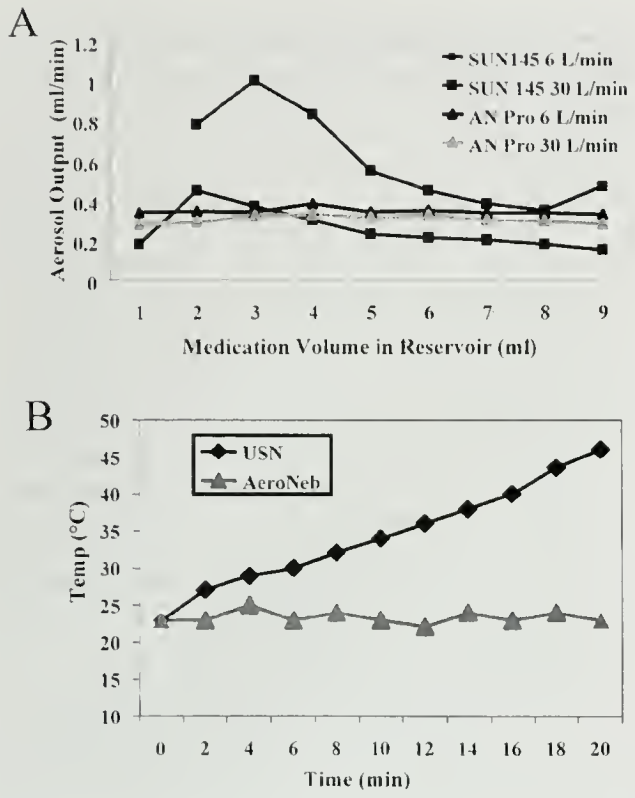


Fig. 7. A: Effect of gas flow rate and medication volume on the output of aerosol by the Aeroneb Pro (AN Pro) and Siemens Ultra Nebulizer 145 (SUN 145) ultrasonic nebulizer. The gas flow rate and medication volume influence the output from the ultrasonic nebulizer. The highest ouput was achieved with a flow of 60 L/min and medication volume between 2 and 4 mL. In contrast, aerosol output from the Aeroneb Pro was not influenced by those factors.[11] B: Solution temperature change during operation of the Aeroneb Pro and SUN 145. Solution temperature change during 20 minutes of operation with the Aeroneb Pro was significantly less than that with the SUN 145 ($p < 0.01$). (Adapted from Reference 11.)

and at a higher level than the connection to the ventilator circuit). The dead volume was 0.2–0.4 mL in the Aeroneb Pro versus 0.8–1.2 mL in the SUN 145.[11] Though both systems delivered comparable amounts of aerosol to the distal end of the endotracheal tube during mechanical ventilation, heat generation in the medication reservoir over 20 min was significantly lower in the Aeroneb Pro ($2 \pm 1°$ C) than in the SUN 145 ($24 \pm 3°$ C) (see Fig. 7).[11]

In another investigation the Aeroneb Pro was compared with the Siemens SUN 145, the Puritan Bennett ultrasonic EasyNeb, and 2 jet nebulizers (Airlife Misty Neb and Salter Labs 8900).[12] Each nebulizer was placed in the inspiratory limb of a heated, humidified ventilator circuit. A Puritan Bennett 760 ventilator provided controlled mechanical ventilation, using adult ventilator settings. Each nebulizer was filled with 3 mL of albuterol sulfate solution (0.083%), and the aerosol was collected by an absolute filter connected to the end of an endotracheal tube (8.0 mm inner diameter). Drug delivery with the SUN 145 and Aeroneb Pro was more than 4-fold higher than that with the jet nebulizers.[12] Furthermore, the efficiency of the Aeroneb Pro in delivering aerosol to the distal end of the endotracheal tube improved to approximately 40% of the nominal dose when a device producing a finer aerosol was used in conjunction with 0.5 mL of albuterol solution placed in the nebulizer.[12] This improvement in the efficiency of the Aeroneb Pro was attributed in part to the ability of the device to aerosolize the solution almost to the last drop, so that dead volume was negligible.[12]

Using a simulated adult breathing pattern, the amount of drug delivered to filters by the Aerodose Inhaler was compared to that by the PARI LC Plus.[13] Aerosol particle size distribution from the Aerodose Inhaler (VMD $\pm$ geometric standard deviation $= 4.3 \pm 2.1$ $\mu$m) was comparable to that from the PARI LC Plus ($4.8 \pm 2.3$). Because the Aerodose Inhaler is breath-actuated and has a very low dead volume ($< 5$ $\mu$L), the nominal dose required in the Aerodose Inhaler to achieve comparable drug delivery was one fifth of the nominal dose in the PARI LC Plus.[13] Moreover, the treatment time was less with the Aerodose Inhaler ($\leq 2.5$ min) than with the PARI LC Plus (approximately 10 min).[13] Thus, use of the Aerodose Inhaler in place of the PARI LC Plus could reduce the nominal dose and treatment time without compromising drug delivery and clinical response.

The NE-U03 and NE-U22 have also been shown to produce aerosols with the majority of particles in the fine particle fraction (MMAD $< 4.7$ $\mu$m). These devices can aerosolize up to 70% of the volume of solution placed in the nebulizer.[14]

With ODEM's TouchSpray, altering the diameter and geometry of the perforations in the membrane modifies the characteristics of the aerosol.[15] The TouchSpray devices produce aerosols with MMAD of 2.1 or 2.7 $\mu$m, with $> 80\%$ of the particles in the aerosol being $< 5$ $\mu$m.[15]

### In Vitro Comparisons of Efficiency in Aerosolizing Suspensions

A simulated pediatric breathing pattern was employed to test delivery of drug suspensions with the Aerodose Inhaler and the PARI LC Plus.[16] Budesonide suspension contains irregularly shaped drug particles with mass median sizes of 2.2–2.9 $\mu$m suspended in an aqueous medium (0.25 mg/mL). With equal amounts (2 mL) of budesonide suspension, the dose in the fine particle fraction was approximately 3-fold higher with the Aerodose Inhaler,[16] mainly because of its finer particle size and lower dead volume.

The ability of the NE-U22 to aerosolize budesonide suspension was also determined in vitro,[14] and its dead volume and distribution of particle sizes tend to be some-

what larger than that reported above with the Aerodose Inhaler. For example, the MMAD from the NE-U22 (using 2 mL of budesonide suspension) was 4.8 $\mu$m, and 30% of the volume remained in the filter, medication container, and vibrator after the treatment.[14]

Smart et al reported that both solutions and suspensions could be efficiently aerosolized with the TouchSpray and that the majority of particles were in the fine particle fraction.[15] TouchSpray devices could be modified to produce aerosols of budesonide suspension (5 mg/mL) that had MMAD as low as 2.2 $\mu$m.[15]

### Scintigraphic Evaluation of Pulmonary Deposition of Aerosol

Pulmonary deposition of inhalable tobramycin radiolabeled with technetium-99m diethylenetriamine pentaacetic acid ($^{99m}$Tc-DTPA) was compared in 9 healthy subjects.[17] On 2 separate days each subject received, in a randomized order, a standard label dose of 5 mL (300 mg) of radiolabeled tobramycin from either the PARI LC Plus Neb with Pulmo-Aide compressor or 1 mL (60 mg) of radiolabeled tobramycin from the Aerodose Inhaler. Gamma camera images of the lungs revealed that the PARI LC Plus nebulizer delivered 9.1 $\pm$ SD 2.2% of the nominal dose to the lungs, whereas the Aerodose delivered 35.4 $\pm$ 10.5% of the nominal dose. Despite using one fifth of the dose of tobramycin with the Aerodose Inhaler, the amount of drug deposited in the lung was similar (21.2 $\pm$ 6.3 mg with Aerodose vs 27.2 $\pm$ 6.7 mg with PARI LC Plus). Moreover, the nebulization time was reduced from approximately 20 min with the PARI LC Plus to approximately 6 min with the Aerodose Inhaler.[17] That study supports earlier in vitro observations that the Aerodose Inhaler has a greater efficiency for drug delivery to the lung and that similar drug delivery could be achieved by decreasing the nominal dose to one fifth that employed in a conventional jet nebulizer.

With the TouchSpray device more than 80% of the liquid $^{99m}$Tc-DTPA placed in the device could be delivered to the lung of a healthy volunteer.[18]

### Clinical Evaluation of Devices

Concerns have been expressed about drug dose with new devices that have a much higher efficiency of delivering aerosol to the respiratory tract. Administering the standard dose of a drug with these devices might cause adverse effects. Clinical studies are needed to determine the appropriate drug doses with these devices.

A randomized, observer-blinded, cumulative-dose, 3-period crossover study was conducted with 24 patients with moderate to severe asthma (forced expiratory volume in the first second [$FEV_1$] 30–70% of predicted, with $\geq$ 15% reversibility after albuterol inhalation).[19] On separate days, patients received 4 doubling doses of albuterol with each of the study devices (62.25–498 $\mu$g with the AeroDose Inhaler; 312.5–2,500 $\mu$g with the PARI LC Plus; and 100–800 $\mu$g with the Ventolin Evohaler MDI). Patients were randomized into 1 of 6 treatment sequences to receive all 3 inhalation treatments in a balanced crossover design. $FEV_1$ increased by more than 300 mL or $>$ 15% from baseline with all doses except the lowest dose from the Ventolin MDI. For all spirometric variables the dose/response curve for PARI LC Plus and Ventolin MDI were similar. In contrast, the Aerodose Inhaler produced bronchodilator efficacy comparable to the PARI LC Plus while using one fifth to one tenth of the nominal dose.[19] No clinically relevant systemic effects were observed on plasma potassium level, heart rate, or QTc interval, even at the highest dose levels, with any of the devices or doses. Thus, with the Aerodose Inhaler the nominal dose of bronchodilator solution could be reduced by a factor of 1:5 or 1:10 (compared to the PARI LC Plus) without compromising bronchodilator efficacy or safety.

A prospective, randomized, investigator-blinded, 5-way crossover study compared the response to ipratropium bromide delivered via Aerodose Inhaler versus via PARI LC Plus in patients with stable chronic obstructive pulmonary disease.[20] Response to ipratropium bromide solution (0.2%) with the Aerodose Inhaler (0.05, 0.1, and 0.2 mg) or placebo (0.9% saline) given via Aerodose Inhaler were compared with the standard dose of 0.5 mg delivered via PARI LC Plus. The area under the curve for $FEV_{1\ 0-4\ h}$ (ie, during the 4 hours following administration) and peak change in $FEV_1$ with 0.1 mg and 0.2 mg of ipratropium bromide with the Aerodose Inhaler were similar to those obtained with 0.5 mg of ipratropium bromide with the PARI LC Plus. The area under the curve for $FEV_{1\ 0-4\ h}$ and peak change in $FEV_1$ in response to the 0.05 mg dose with the Aerodose Inhaler were lower than those with the PARI LC Plus.[20] These findings lend further support to the view that the higher efficiency of lung delivery with the Aerodose Inhaler could allow substantial reduction of dose without compromising efficacy.

### Aerosolization of Insulin

The ability to vary particle size distribution by altering the size of the plate's aperture was investigated.[21] Two types of Aerodose Inhaler, one with VMD of 3.5 $\mu$m and another with VMD of 4.5 $\mu$m, were selected. With the larger aerosol particle size the aerosolization rate of a commercial insulin formulation was higher, but the fine particle fraction was lower. That study demonstrated that the particle size distribution could be varied by changing the size of the aperture plate holes.[21] Drug delivery to the respiratory tract could thus be precisely controlled by using different size aperture holes for different clinical applications.

Kapitza et al investigated the impact of particle size and aerosolization time with the Aerodose Inhaler on the metabolic effect of an inhaled insulin aerosol.[22] They used Aerodose Inhalers that produced aerosols of 2 different particle sizes but both with MMAD $< 3$ $\mu$m. One of the inhalers produced a fine aerosol, whereas the other produced a very fine aerosol. Two different aerosolization times were employed (for either the first 2 s of a 5 s inhalation or for 4 s of a 5 s inhalation). Thirteen healthy volunteers were involved in a euglycemic glucose clamp study (180 min baseline, clamp level 5.0 mM/L, continuous intravenous insulin infusion 0.15 mU/kg/min). Each subject received 0.15 U/kg regular insulin on the first study day. On the following 4 study days, 1.5 U/kg of inhaled insulin was administered as a fine or very fine aerosol, using either 2-s or 4-s delivery times. Glucose infusion rates were measured for the subsequent 6 hours. Inhaled insulin had a faster onset of action (defined as time to half maximum action) than subcutaneous injection. Aerosolization time, but not differences in particle size distribution, significantly influenced the metabolic effect of inhaled insulin.[22] The 4-second aerosolization time resulted in significantly higher maximum metabolic action, total metabolic activity, and relative biopotency than the 2-second aerosolization time.[22] The metabolic effect of inhaled insulin was therefore changed by altering the aerosol particle size distribution and aerosolization time per breath. The highest relative biopotency was achieved with the combination of the very fine particle size and the 4-second aerosolization time.[22] The ability to customize delivery by changing aerosol characteristics would allow rational selection of an optimal inhaler configuration in future studies.

ODEM's TouchSpray device can efficiently aerosolize human insulin (Velosulin, 100 U/mL) and bovine serum albumin (40 mg/mL) into fine particles with mean recovery rates $> 90\%$.[23]

### Aerosolization of Deoxyribonucleic Acid

Deoxyribonucleic acid (DNA) is substantially degraded during nebulization with conventional jet nebulizers.[24] Smart et al determined whether ODEM's TouchSpray device could efficiently nebulize plasmid DNA.[25] Two mammalian expression plasmids harvested from *Escherichia coli* DH5$\alpha$ strains (pRep5 and pCDNA-HEW) were tested. PRep5 is a circular plasmid DNA (11.0 kilobase pairs [kb]), whereas the pCDNA-HEW is a digested, linearized DNA segment (4.5 kb). Volumes of 300 $\mu$L pRep5 and pCDNA-HEW 1000 $\mu$L were aerosolized at concentrations ranging from 2.5 to 100 ng/$\mu$L. The particles in the aerosol generated were mostly in the fine particle fraction.[25] Most (approximately 90%) of the circular pRep5 plasmid DNA molecules and approximately 50% of the pCDNA-HEW molecules were degraded during nebulization.[25] Recovery of intact DNA was improved by either linearizing pRep5 or by using smaller fragments of pCDNA-HEW (1.5 kb vs 3 kb).[25] More than 90% of the 1.5 kb linear pCDNA-HEW plasmid was recovered intact after aerosolization.[25] The smaller and linearized DNA molecules may be more flexible and less easily degraded by the torsional stresses encountered during aerosolization.

### Limitations/Drawbacks of Vibrating Plate/Mesh Devices

Obviously, at present clinical experience with routine use (or misuse) of these devices (that create aerosol with a vibrating mesh or plate with multiple apertures) by patients outside the setting of clinical trials is limited. However, most patients can be trained to use these new devices without difficulty. The cost of these devices is much higher than that of conventional jet nebulizers but may be lower than that of some ultrasonic nebulizers. The cost may vary but will probably be $200 to $300 for each device. That cost may decline as consumer demand increases. Concerns have also been expressed about blockage of the minute apertures with drug particles, particularly when suspensions are aerosolized. This problem may be more important for some devices than for others. Regular cleaning of the device needs emphasis. Because of the higher efficiency of drug delivery to the lung, the drug doses and volume of solution used need to be reduced to prevent adverse effects. The "all-purpose" nebulizer may become obsolete, with each new device being marketed with a specific drug. Manufacturers may not find it attractive to invest their resources in administering commonly used drugs, opting instead to deliver more expensive "designer" drugs with this new technology. Such an approach could limit the applications for this new technology.

### Summary

Several electronic nebulizer devices that use a vibrating mesh or plate with multiple apertures to generate a fine-particle, low-velocity aerosol have been marketed or will shortly become available for clinical use. These devices have a high efficiency of delivering aerosol to the lung, such that the nominal dose of drugs to be administered could be substantially reduced. Moreover, the dead volume is negligible, so there is potential to improve the cost-effectiveness of administering expensive medications. Because these devices nebulize at a faster rate than conventional jet or ultrasonic nebulizers, the duration of each treatment could be shortened. These devices efficiently nebulize solutions and suspensions; they have been successfully used for aerosolizing insulin, other proteins and peptides, and fragments of DNA. These versatile and portable devices could be employed for a wide variety of

clinical applications, including the delivery of aerosols for systemic therapy and gene transfer.

Devices that use a vibrating mesh or plate with multiple apertures to generate an aerosol from a liquid medication have overcome many of the limitations associated with conventional jet and ultrasonic nebulizers. These devices have a high efficiency of delivering drugs to the respiratory tract and the versatility to modify the aerosol characteristics according to the clinical application for which they are employed. With these devices clinicians will be able to precisely control drug delivery to the respiratory tract.


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### Discussion

**Rau:** Rajiv, thank you for a fascinating presentation. Why does the solution temperature *not* increase in the Aerogen or Omron devices? Is it the lower frequency, or lower power and amplitude of the motion? Where do they get rid of the energy that we normally see as heat in the traditional ultrasonic nebulizer?

**Dhand:** With the standard ultrasonic nebulizer the piezoelectric crystal focuses energy onto the liquid. It's a high energy and it's focused, and that's why heat is generated. In the Aerogen and Omron devices the liquid is not really energized. With the Aerogen technology the piezoelectric crystal contracts and expands, and there is about 1-micron of displacement of the

domed aperture plate within the liquid. Because of that minimal movement very little energy is required and therefore very little heat is generated. With the Omron NE-U03 the energy requirement is very much lower. Standard ultrasonic nebulizers operate in the range of 1.5 MHz, whereas the NE-U03 operates at only 65 kHz. The NE-U22 requires more energy but it is still in the kilohertz range; I believe it's about 135 kHz. Also, again, the energy is not directed toward the medication. In the case of the NE-U22, it's the *horn* that vibrates, and that's what moves the liquid through the mesh.

**Smaldone:** The older Omron devices were very sensitive to maintenance; there was a video (that was hard to follow) on how to clean it. The newer devices, I think, are more robust. So I'm wondering about clogging and cleaning. There are a lot of little holes in there.

**Dhand:** That is an excellent point. Obviously, if you're using a suspension that contains larger particles, there will be a chance that the holes get clogged up. However, Jim [Fink] told me that with the Aerogen device they've not experienced that problem, and it might be that the pumping action itself is a cleaning action for the holes. Certainly when the devices come into clinical use we might find other problems, but with the in vitro and clinical testing that has not been a problem. In the devices we used with our patients with chronic obstructive pulmonary disease, we didn't see that problem. The devices aerosolized very efficiently.

**Fiel:*** I have a question about the reliability of some of these devices. Based on the range of solutions that might be used in routine practice, whether it be with proteins or not, are certain devices better than others in relation to reliability or the way they work? Whether it be the vibrating horn or some other technology or, as Gerry Smaldone pointed out, small particles, do you have a sense of one that *might* be better, at least theoretically, from your experience?

**Dhand:** I don't have any personal experience with the Omron NE-U22, but I do have experience with the Aerogen device, and I believe that it will work well with suspensions, proteins, and even peptides.

**Geller:** Great presentation, Rajiv. I had some experience with the Omron MicroAir device. We measured laser particle size of around 7.5–8 microns MMAD. The device was engineered to be *equivalent to* older devices, not *better than*, in terms of respirable or fine particle dose. It nebulizes almost everything in the cup, but the particle size was much larger, so you end up with the same respirable dose.

**Dhand:** I think one of the changes they made was to the characteristics of the plate. The original device had a ceramic plate, and this one has an alloy, electroplated plate that will probably give a better and more uniform particle distribution.

**Geller:** We also did a "proof of concept" trial with TOBI [inhalable tobramycin solution] and showed that it took almost 100 mg of TOBI in the Aerodose versus 300 mg in the PARI LC Plus to get similar sputum and serum levels. That paper will be published in *CHEST* soon. One of the engineering problems encountered is that the Aerodose was not really meant to be used with tidal breathing. During the study the patients were tidal breathing, so one of the problems that occurred was that some of the tobramycin would get into the electronics of the device and gum it up. The device wasn't reusable at that point. And that's just one of the engineering issues that can be worked through over time (I hope) to make that device into a tidal breathing device. When you take a device that is meant to be used one way and try to use it in a different way, it might not always work.

**Dhand:** That's a very valid point. Obviously, we don't have all the answers right now. But certainly, we're on the right track, and I believe these devices represent an important advance.

**O'Riordan:** How do they change the particle size for, say, insulin versus albuterol? Is that a function of the vibration frequency?

**Dhand:** No, it has to do with the size of the holes. You can vary the size of the holes and thereby the particle size.

**Dolovich:** Siemens came out with a nebulizer that was an integral part of their ventilator circuitry. They had a large-cup device and a small-cup device. The large cup was ineffective because the coupling was nonexistent for the fluid in the cup. Do you see any of these other devices being used in in-line ventilator circuits?

**Dhand:** I'm going to defer that question to Jim [Fink], because I think he did some testing with that device.

**Fink:*** The Aeroneb Pro is the application of the Aerogen aerosol generator technology designed for use with mechanical ventilation. Besides being relatively small and light, so that it can be placed closer to the patient in the ventilator circuit, the orifices in the aerosol generator are so small that it does not perceptibly leak gas when the nebulizer reservoir is open to the atmosphere. The Aerodose inhaler used in the TOBI study was an early version of our breath-actuated inhaler,

* Stanley B Fiel MD, MCP Hahnemann University, Philadelphia, Pennsylvania (discussant for Monaghan Trudell, Syracuse, New York).

* James B Fink MSc RRT FAARC, Aerogen, Mountain View, California.

which was designed for a deep breath and breath-hold maneuver, so that it needed to be "smoked" by the patient for use with tidal breathing. The newer version of the Aerodose inhaler can be used for deep breath or tidal breathing.

**MacIntyre:** We've heard 2 presentations in this conference about devices that improve lung deposition by 2 or 3 times over what we're used to. Is it just because you're making smaller particles and that the aerosol can be delivered with tidal breathing? Is that all there is to it? A better, cleaner, smaller aerosol cloud?

**Dhand:** Also a slower-moving cloud, more uniform particle size distribution, and with the Aerodose, I think the breath-actuation is a very important part of it.

**Smaldone:** Nebulized drug delivery during tidal breathing has certain advantages, and the slow particle velocity is very important because it helps minimize oropharyngeal deposition. And the less the dead volume, the better the efficiency. To me the difference between the old technology and the new is the difference in dead volume. These mesh devices are one of the first attempts to minimize dead volume, although the non-nebulizer "squirters" such as AERx also have very small dead volume. Once you get rid of the dead volume, then all the advantages of nebulizers come out, in terms of their ability to deliver aerosol to the lung.

**Gomez:** I would point out that these nebulizers we're discussing are all "ultrasonic" nebulizers, because they all operate above 20 kHz, even though the community seems to make some distinctions.

**Fink:** I'm not sure that everything that uses a piezoelectric ceramic element is best described as ultrasonic. The Aerogen technology runs at a lower frequency, does not generate heat, and uses a totally different mechanism to generate aerosol than do standard ultrasonic nebulizers. It seems that this is sufficient to merit a differentiating name for the principle mechanism of aerosol generation.

**Gomez:** I agree. They're quite different. But both rely on ultrasonic excitation. Perhaps we should use a better-suited terminology to highlight the distinctions among the various types.

I was interested in that plate with the converging nozzles. Do you know how they make it? You seemed to indicate that it's of the vibrating-orifice type, which should produce strictly single-size droplets. If that's so, why the spread in size distribution? Is it because the flow rates are not uniform across the single holes?

**Fink:** The Aerogen aperture plate is created through an electroplating process that allows us to build the funnel-shaped apertures with a specified exit diameter, depending on application. The diameter of the aerosol particle is directly related to the aperture exit diameter. The devices you referred to as monodisperse may use one aperture to produce aerosol. With approximately 1,000 apertures on a domed plate pumping aerosol, we tend to produce aerosols that are not quite monodisperse, with a geometric standard deviation of 1.9–2.0 $\mu$m rather than 1.4 $\mu$m.

**Dennis:** Gerry [Smaldone] said that we have increased efficiency because we have smaller dead volume (which is true)-and longer nebulization time: we need to train and educate people that a longer nebulization time isn't necessarily bad; if a device becomes very efficient, then you can stop nebulization when the dose is right. We're still nebulizing a standard ampule volume.

These devices also have the potential of much greater efficiency because they don't waste aerosol to the environment. So for some of them you *only* get the aerosol inhalation. I think that's as important as the small dead volume.

The third thing is that these devices don't use compressed air. So if you've measured a standard particle size with the laser, that measure is really distanced from the conditions when the patient inhales. The particle size measurement method should involve the inhalation system that will be used by the patient, so you inhale all these aerosols that are not being generated in a saturated cloud—they just come into being and are pulled into ambient air, and that ambient air will become saturated from water vapor drawn from the droplets. If you have a very *small* amount of emission from these devices, all the liquid will evaporate and you'll end up with dry powder. So, tactically, this could prove to be a very good avenue for producing dry powder inhalers.

On the down side, with devices that have variable output (it might be 30 or 50 or 100 mL/min) there will be various amounts of evaporation, so you lose control of particle size. Taking this observation further, the rate of total aerosol output ultimately controls particle size from bolus devices when they start getting down to low outputs, below 50 mL/min. If the bolus output is higher than about 50 $\mu$L, the evaporation doesn't really matter, because it is minimal compared to the overall aerosol output. In any case, the way the patient uses the device must be taken into consideration in measuring particle size.

This is really a warning to users and manufacturers: that with variable output you're going to have variable droplet size. One of the challenges to manufacturers is to overcome the technical difficulties and make devices that are not variable in output. I think there are technical difficulties in making all the devices right now, but these are being overcome—there are 3 or 4 separate company developments, so some of them are going to make it to market. I think these will be issues when they do come to market.

# The Electrospray and Its Application to Targeted Drug Inhalation

Alessandro Gomez PhD

**Introduction**
**Experimental System and Methods**
**Liquid Break-Up, Droplet Dispersion, and Monodispersity**
**Required Liquid Physical Properties and Scaling Laws**
**Electric Charge: Consequences and the Need to Neutralize the Droplets**
**The Need for Multiplexing**
**The BattellePharma Electrospray Nebulizers**

**This review explains the fundamentals of electrostatic spray (electrospray) atomization, with emphasis on operation in the so called cone-jet mode, which produces droplets with a very narrow size distribution. Since the control of droplet size is key to maximizing distal lung deposition, the electrospray should be well-suited to targeted drug inhalation. Electrospray droplets are a few micrometers in diameter, but they originate from a much larger nozzle, which allows nebulization of suspensions without clogging. Also discussed are: the physical principles of the break-up of the liquid ligament; droplet dispersion by Coulombic forces; and the most important scaling law linking the droplet size to liquid flow rate and liquid physical properties. The effects of the most critical of those properties may result in some restrictions on drug formulation. Droplets produced by electrospray are electrically charged, so to prevent electrostatic image forces from causing upper respiratory tract deposition. The charge is neutralized by generating a corona discharge of opposite polarity. Briefly discussed are the main differences between the laboratory systems (with which the electrospray has been quantitatively characterized during research in the past 10 years) and commercial electrospray inhalers under development at BattellePharma. Some remarkable miniaturization has incorporated liquid pump, power supply, breath activation, and dose counter into a palm-size portable device. The maximum flow rates dispersed from these devices are in the range of 8–16 $\mu$L/s, which makes them suitable for practical drug inhalation therapy. Fabrication is economically competitive with inexpensive nebulizers. Dramatic improvements in respirable dose efficiency (up to 78% by comparison with commercial metered-dose inhalers and dry powder inhalers) should ensure the commercialization of this promising technology for targeted drug inhalation.** *Key words: targeted drug delivery, inhalation, nebulization, electrospray, electrostatic spray, aerosol.* [Respir Care 2002;47(12):1419–1431]

## Introduction

Deposition of inhaled aerosol occurs by 3 physical mechanisms: inertial impaction, gravitational sedimentation, and Brownian diffusion. Targeting deposition to specific areas of the respiratory tract can be achieved by controlling the size of the aerosol droplets, which in turn affects the dep-

Alessandro Gomez PhD is affiliated with the Department of Mechanical Engineering, Yale University, New Haven, Connecticut.

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Correspondence: Alessandro Gomez PhD, Department of Mechanical Engineering, Yale University, PO Box 208286, New Haven CT 06520-8286. E-mail: alessandro.gomez@yale.edu.

osition mechanism.* The objective is to deliver the drug directly to the site of action and thereby minimize the dose required to achieve an adequate response to the inhalation therapy. This approach may be particulary advantageous when cost and/or adverse effects are of concern.

Aerosol generators for drug inhalation range from relatively simple, inexpensive types to large, expensive, and complex systems.[3] Examples of the first category are jet nebulizers, pressurized metered-dose inhalers, and dry powder inhalers, which generate a polydisperse distribution of aerosol droplets or particles. At the other end of the spectrum are much more complex alternatives, such as the modified Sinclair-La Mer generator,[4] capable of generating (by condensation methods) monodisperse particles to be stored in a large volume prior to inhalation. However, construction and operation of that type of generator is complex and confines its use to research applications. A few liquid nebulization technologies have recently emerged that offer control of the distribution and size of the aerosol droplets, are amenable to miniaturization, and are sufficiently inexpensive to provide appealing alternatives to traditional inhalers. The present review focuses on technologies that use one or more electrosprays to nebulize liquid formulations. The term *electrostatic spray* (also known as *electrohydrodynamic spray* or *electrospray*) is used in this review with reference to systems in which the dispersion of the liquid relies *solely* on its electric charging, so that nebulization and gas flow processes are relatively uncoupled. The potential for an electrospray-based technology for targeted inhalation was first recognized by Tang and Gomez.[5] Recent developments at BattellePharma have generated considerable interest in this approach. Figure 1 shows the latest prototypes of inhalers developed by BattellePharma, including a portable device and a benchtop alternative. High-voltage electricity supply, pumping, droplet discharging, and breath activation have been folded into a successfully miniaturized system.

To be able to rely on the extensive characterization in the literature and to avoid being encumbered by the "bells and whistles" of commercial devices, attention here is restricted to a particular type of electrospray that captures the salient features of the BattellePharma inhalers. Such a spray can be implemented very simply by feeding a liquid

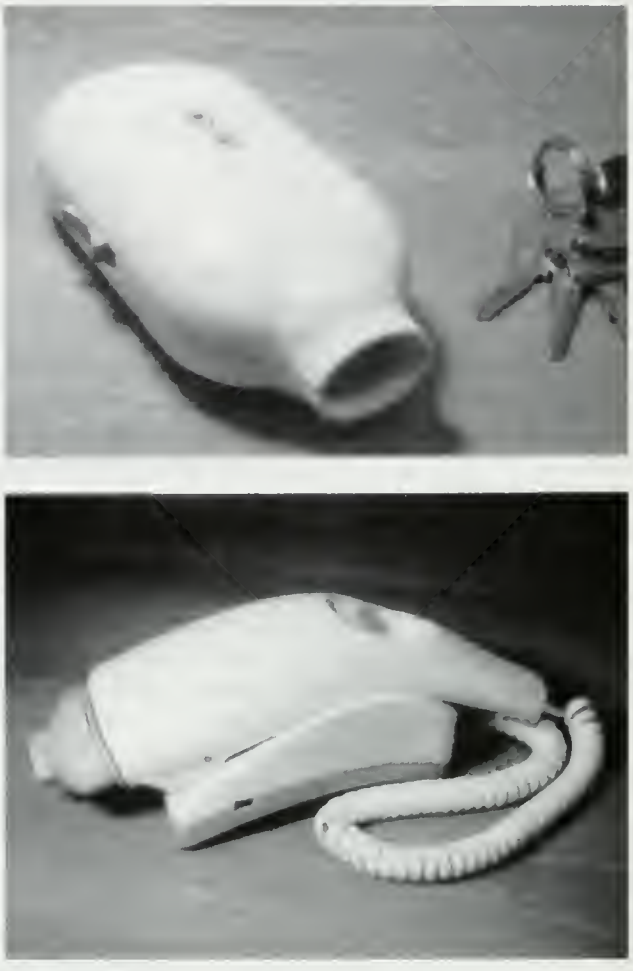

Fig. 1. Prototypes of the portable inhaler (top) and of the benchtop device (bottom) developed by BattellePharma, as a result of design evolutions through the summer of 2002. (Courtesy of Donna Palmer and William Zimlich, BattellePharma, Columbus, Ohio.)

* Total lung deposition, when plotted versus particle diameter, exhibits a minimum at around 0.5 $\mu$m.[1] Even though substantial deposition could be achieved by Brownian diffusion with particles smaller than 0.5 $\mu$m, that deposition would not be targeted, since such ultrafine particles would be likely to deposit anywhere in the respiratory tract. For particles larger than 0.5 $\mu$m, inertial impaction and gravitational sedimentation prevail, since particle diffusion coefficients are too small for diffusion to be substantial. The optimal size range for maximal deposition in the deep lungs is 2–5 $\mu$m.[2] For such particles, sedimentation plays an important role only when gas velocities are sufficiently low, since sedimentation velocities are on the order of $10^{-2}$ cm/s (for a particle density of 1 g/cm$^3$). These conditions are met in the peripheral airways and the pulmonary area (eg, airway generations 16–23).[2] But before sedimentation can play a substantial role in deposition, particles must reach the distal lung region. To that end, control of droplet inertial behavior is critical. Physically it is required that the particle Stokes number, defined as:

$$St = \frac{\tau_p}{\tau_f} = \frac{\rho_p D^2}{18\mu} \times \frac{1}{\tau_f} \qquad (1)$$

be sufficiently small (< 0.1). This number is the ratio of a particle's relaxation time, defined in terms of the particle density ($\rho_p$), the diameter (D), the gas dynamic viscosity ($\mu$), and a characteristic fluid time ($\tau_f$). The strong dependence of the Stokes number on size implies that targeted deposition can be achieved only through control of aerosol droplet size and size distribution, which depends on the type of aerosol generator used. For example, a nebulizer that produces an aerosol with a substantial "tail" of large droplets in the distribution would be unsuitable, since the large droplets, which contain a considerable fraction of the liquid volume aerosolized, would have relatively large Stokes numbers and would impact in the upper respiratory tract. The Stokes number relationship also implies that nebulization must be sufficiently "soft" to keep the fluid time ($\tau_f$) large.

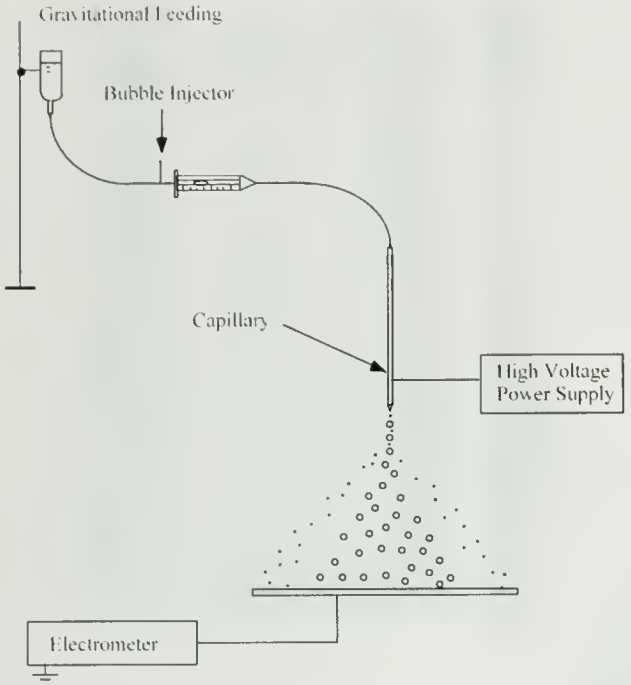


Fig. 2. A simplified electrospray system for laboratory studies. (From Reference 5, with permission.)

with sufficient electrical conductivity and moderate surface tension through a capillary tube and charging it by a metal electrode in contact with the liquid and maintained at several kilovolts relative to a ground electrode a short distance away. This type of electrospray has the additional feature of a tight control of the size distribution of the aerosol, as will be shown below. The objective is to review the physical principles underlying the operation of such an electrospray and to examine the potential limitations imposed by certain requirements in the physical properties of the aerosolized liquid, which ultimately may constrain drug formulation. This review draws heavily from the work of Tang and Gomez.[5,6]

## Experimental System and Methods

The simple schematic in Figure 2 represents most of the principal components of an electrospray system. Most of the data discussed here were collected with such an apparatus. Relevant differences with the BattellePharma system are discussed below. The system consists of a stainless steel capillary tube charged at a high electric potential, between 10 and 20 kV, and a ground electrode positioned 3 cm away, perpendicular to the tube. For simplicity the liquid is gravitationally fed from a reservoir into the tube. The flow, which is controlled by changing the height of the reservoir relative to the tube, is measured by timing the displacement of a gas bubble injected into the liquid line through a calibrated micro-syringe. More elaborate pumping and metering systems are typically used in practice. The current carried by the electrospray is monitored by an electrometer connected to the ground electrode.

The spray behavior is monitored by 2 optical diagnostic techniques: phase Doppler anemometry and flash illumination. The phase Doppler anemometry system (Dantec Electronics, Portbury, United Kingdom) determines the size and the velocity of the droplets by light scattering. The shadowgraph flash illumination system monitors the stability of the electrospray and highlights details of the break-up process. It consists of a nanosecond flash lamp (Xenon, Woburn, Massachusetts) and a stereo zoom microscope, the latter coupled to a closed-circuit digital camera (Pulnix, Sunnyvale, California). The nanosecond flash allows us to freeze the motion of the droplets. Alternatively a 10 ns pulse laser illumination is used to photograph the electrospray scattering with a digital camera.

## Liquid Break-Up, Droplet Dispersion, and Monodispersity

Figure 3 shows an ethanol drop suspended at the outlet of a metal tube. When an appropriately intense electric field is applied to the tube, by providing a voltage on the order of kilovolts, the liquid meniscus is drawn into a conical shape with a fine spray emerging from it (the electrospray), as shown in Figure 3B, which is an instantaneous picture under the illumination of a 10 ns pulse laser. Figure 4 shows a close-up view of the highlighted rectangle in Figure 3B, which reveals details of the break-up of the liquid ligament. The sequence of events leading to the formation of a spray with nearly uniform droplet sizes is observed over a broad range of operating conditions and droplet sizes and is typical of all electrosprays with narrow droplet size distributions. The images in Figure 4 pertain to a heptane electrospray that produces droplets sufficiently large to be photographed with an optical microscope.[7] First (Fig. 4A) the liquid exits the cone formed at the outlet of the charged tube as a thin ligament that is stable for a short distance. This ligament then breaks up into droplets (Figs. 4B and 4C), which typically exhibit a bimodal distribution of larger primary droplets and smaller satellite droplets. Farther downstream, the droplets become nearly monodisperse as the smaller satellites, driven by the electric field, migrate rapidly away from the axis (Fig. 4C). The primary droplets left behind are quasi-monodisperse. They move downstream, are gradually displaced radially, and form a wavy signature pattern under instantaneous illumination (Fig. 4D). They eventually form a fan that coincides with the electrospray visible under appropriate illumination.[7]

Figure 4A shows that, before break-up occurs, axisymmetric varicose waves propagate along the ligament because of naturally occurring disturbances. Such waves lead

Fig. 3. Top: Ethanol dripping from a metal tube at a low flow rate. Bottom: Under an applied voltage (as observed under pulsed laser illumination) the pendulant drop assumes a conical shape and emits a liquid ligament that disperses into droplets.

to a change in the pressure distribution along the liquid ligament, which is associated with the presence of surface tension. As a result, the liquid is driven away from the ligament restrictions, ultimately yielding the pinching of the continuous ligament into discrete droplets. The ratio of primary droplet to ligament diameter was measured at about 1.9, in good agreement with experimental findings of others on similar sprays.[8–10] This result also confirms extensions of Rayleigh's theory[11] on the stability of uncharged capillary jets,[12,13] which showed that even at relatively large charge levels the predictions of the theory are not significantly altered. Thus, electrification is responsible for extruding the liquid at the outlet of the tube into a liquid ligament through electrohydrodynamic processes in the liquid cone. The droplet size is controlled indirectly by determining the formation and diameter of the liquid ligament. Since the ligament diameter is much smaller than the tube bore, micron-size droplets can be generated from relatively large orifices without clogging, which is a unique advantage of this nebulization technique, and even liquid suspensions can be nebulized.

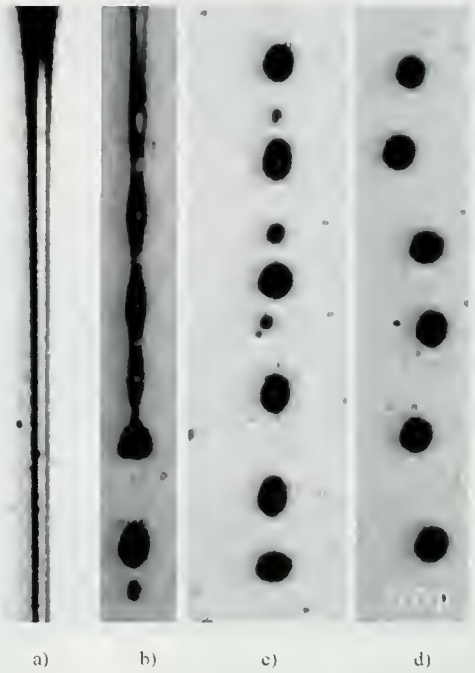


Fig. 4. Details of the break-up process (enlargements of highlighted rectangle in Fig. 3). A: Continuous liquid ligament. B and C: Primary and secondary droplets form downstream of the break-up point. D: Wavy signature pattern of the primary droplets as they begin to disperse under the action of Coulombic repulsion. (From Reference 7, with permission.)

The sinuous pattern in the array of primary droplets in Figure 4D is *not* to be interpreted as indicative of a droplet trajectory. Droplets follow diverging trajectories departing from a common origin where the liquid ligament breaks up. It can be readily shown that a stream of closely spaced droplets, as in Figure 4D, is inherently unstable because of the Coulomb repulsion of droplets charged with the same polarity. If one imposes a small radial displacement on any of these droplets, a radial component of the electrostatic repulsive force in the outward direction "cascades" onto all the neighboring droplets. This effect, coupled with diverging lines of the external field between the tube and the ground electrode, ultimately leads to spray dispersion, as hinted by the wavy signature pattern of the break-up region. Thus, droplet Coulombic repulsion or, equivalently, space charge effects play a crucial role in this region: if only the external field were acting on the droplets, they would predominantly persist in their axial trajectory, without dispersing into a spray.

Satellite droplets are visible in Figure 4D. Once the satellite droplets are displaced radially by small disturbances and/or space charge effects, they can better follow the diverging lines of field because of relatively small inertia and high charge-to-mass ratio.[7] They are thus removed from the core of the spray by electrostatic/inertial separation.

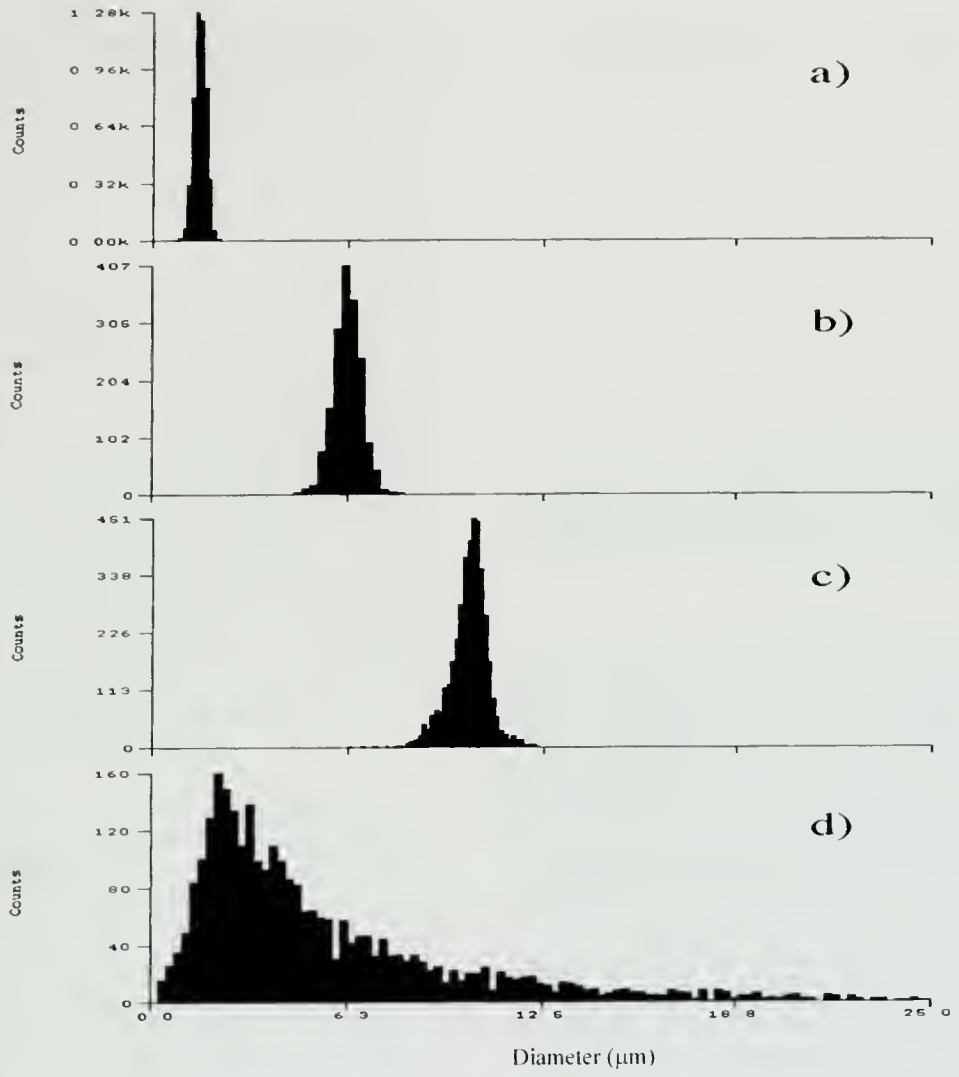


Fig. 5. Typical droplet size distributions of water. A: Electrospray liquid flow rate (ES Q) = 4.67 μL/min; droplet diameter (d) = 2.45 μm; ratio of standard deviation to diameter (SD/d) = 0.12. B: ES Q = 19.2 μL/min; d = 6.11 μm; SD/d = 0.08. C: ES Q = 39.4 μL/min; d = 10.1 μm; SD/d = 0.06. D: Droplet size distribution of aerosol from a Fisons metered-dose inhaler. (From Reference 5, with permission.)

When evaporative effects are substantial, as is the case with relatively volatile liquids nebulized at low flow rates and producing correspondingly small droplets (eg, diameter $< 10$ μm), the distinction between the core and the shroud of the aerosol is less clear. Under those conditions, the smaller droplets in the outer periphery of the spray evaporate faster than the droplets near the spray axis, because of the size-dependent rate of diameter change.[14] Thus the droplet size distribution may broaden somewhat, as the droplets move away from the break-up region. This is typically the case for inhalation sprays.

In view of the morphology of the liquid meniscus in Figure 3, this mode of operation is called *cone-jet mode*.[8] Several other types of electrostatic nebulization are also possible, as shown by Zeleny in the first systematic investigation on the subject[15] and recently by Cloupeau and Prunet-Foch in their comprehensive study.[16] Even though electrospray operation in a practical device may not be always in cone-jet mode, for the purpose of characterizing electrospray behavior it is best to refer to cone-jet mode, because it is well defined, the experimental conditions can be easily reproduced, and it offers optimal control of droplet size and size distribution.

Typical size distributions are measured with the phase Doppler system. Figure 5 shows sample distributions of a few water electrosprays. The mean droplet diameters are 1.4 μm (Fig. 5A), 6.1 μm (Fig. 5B), and 10 μm (Fig. 5C), which were obtained at liquid flow rates of 3.0 , 19.2 , and 39.4 μL/min, respectively. The first distribution was obtained from a saline solution, the others from deionized water. The liquid electric conductivity and surface tension were measured at 1.02 $10^{-6}$ $\Omega^{-1}cm^{-1}$ and 73 $10^{-3}$ N/m,

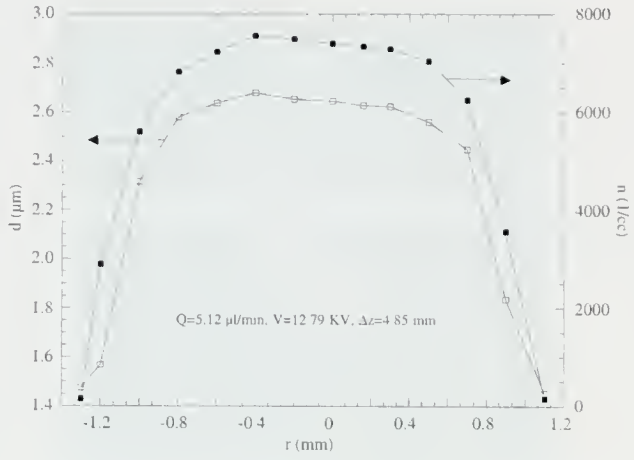


Fig. 6. Mean droplet diameter and number density versus radial coordinate at a fixed axial location where evaporation effects are negligible. Q = liquid flow rate. V = voltage. Δz = change in the distance from the capillary tube. (From Reference 5, with permission.)

respectively, for deionized water. The solution of water plus 0.005% of NaCl by weight had an electric conductivity of 1.2 $10^{-4}$ $\Omega^{-1}cm^{-1}$, all other liquid properties being the same as deionized water. Notice that the droplets generated have diameter orders of magnitude smaller than the tube used in these experiments (inside diameter 0.12 mm, outside diameter 0.45 mm). The relative standard deviation (ie, the ratio of the standard deviation to the mean diameter) is 0.14 for the smallest mean size, 0.08 for the intermediate one, and 0.06 for the largest size. The narrowness of these distributions can be contrasted with the breadth of the distribution of inexpensive commercial nebulizers routinely used for drug inhalation. Figure 5D shows one such distribution, obtained from a metered-dose inhaler. The mean diameter is about the same as that of the distribution in Figure 5B, but the relative standard deviation is now 1.12![*]

To determine whether there are significant variations in droplet size across the spray and if the distributions are uniformly narrow, measurements are performed at various locations in the spray. Figure 6 shows the results of a typical radial scan at a fixed position downstream of the capillary tip. The abscissa is the radial distance from the spray axis, the left ordinate is the mean droplet size, and the right ordinate is the number density. All the size distributions are as narrow as in Figure 5A-C. In the spray core, characterized by the largest concentration of droplets, the mean diameter is approximately constant. A marked decrease in the average droplet diameter is observed only at outer radial locations, where the droplet number density begins to fall off. By ruling out a possible role of droplet evaporation at that location (in view of the short residence time), this behavior is attributable to the electrostatic/inertia separation phenomenon that confines the smaller droplets to the outer periphery of the spray.[5] Figure 6 shows that the bulk of the flow is dispersed into droplets of rather uniform size. Consequently, measurements on the centerline, sufficiently close to the capillary tube to minimize any evaporation effect, should be representative of what is generated at the spray source.

Figure 7 shows some representative distributions obtained with the BattellePharma inhalers. They do not appear as monodisperse as the data in Figure 5. This may be the result of operation outside of the cone-jet mode or of the lack of uniformity among multiple sprays in parallel (see below). Nevertheless, the distributions appear sufficiently narrow for the goal of targeted inhalation and are significantly better than alternative nebulization techniques.

## Required Liquid Physical Properties and Scaling Laws

Correct electrospray behavior, yielding good control of size distribution, up to virtual monodispersity, depends on many variables and experimental features, such as the geometric arrangement of the electrodes, the wettability of the electrospray source, the surrounding gas and its pressure, and the evaporation rate of the solution. Thoroughly describing its behavior in terms of all of those variables is an unrealistic task, possibly requiring an understanding of the system electrohydrodynamics that is lacking at present. On the other hand, if all the above variables are kept fixed, the system behavior can be characterized in terms of a few critical liquid physical properties, once the appropriate electric field is established to obtain the cone-jet mode. Those properties are: the electric conductivity (k), the dielectric constant ($\epsilon$), the viscosity ($\mu$), and the surface tension ($\gamma$). Also critical because of its effect on droplet size is one key operating variable: the liquid flow. In the following discussion, some general scaling laws will be presented to help the user "design" the appropriate solution to obtain the optimal aerosol particle size for deposition in the respiratory tract. These scaling laws have been verified for polar fluids, such as water and alcohols, which are typical excipients. These relationships were derived from dimensional analysis[17,18] and refined by Chen and Pui.[19] The relationships were experimentally tested for a variety of liquids, including water, alcohol, benzyl alcohol, ethylene glycol, and water/alcohol mixtures, spanning a broad range of physical properties, as follows: $\gamma$ = 21–80 dyn/cm, k = 8–700 $\mu\Omega^{-1}$/cm, $\epsilon$ = 12–80, $\mu$ = 0.89–18 cP.

[*] Since some droplet size distributions from commercial devices approach a log-normal distribution, the often-quoted value of interest of their dispersion is the geometric standard deviation (GSD). For comparison, a relative standard deviation (RSD) of 0.10 for a normal distribution is approximately equivalent to a GSD of 1.1 of a log-normal distribution.

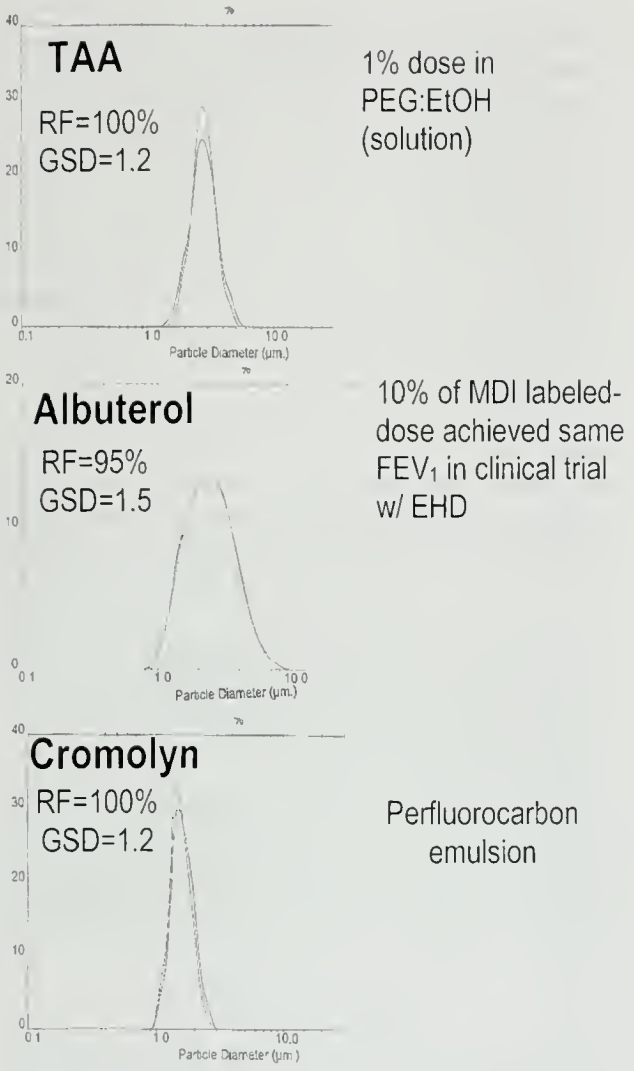


Fig. 7. Sample distributions of 3 drugs electrosprayed by the BattellePharma nebulizers. A: Triamcinolone acetonide (1% dose in a polyethylene glycol and ethanol solution). Respirable fraction (RF) = 100%. Geometric standard deviation (GSD) = 1.2. B: Albuterol. In a clinical trial, 10% of a metered-dose inhaler label dose delivered via electrospray achieved the same forced expiratory volume in the first second. RF = 95%. GSD = 1.5. C: Cromolyn (perfluorocarbon emulsion). RF = 100%. GSD = 1.2. (Data from Donna Palmer and William Zimlich, BattellePharma, personal communication, 2002.)

From a targeted inhalation perspective, critical is the following relationship:

$$D = f(\varepsilon)(Q\varepsilon\varepsilon_0/k)^{1/3} = f(\varepsilon)(Q\tau_e)^{1/3} \qquad (2)$$

which shows a dependence of diameter ($D$) on liquid flow ($Q$), dielectric constant, and liquid electric conductivity. The latter 2 properties appear in the expression of the charge relaxation time ($\tau_e$) denoting the characteristic time

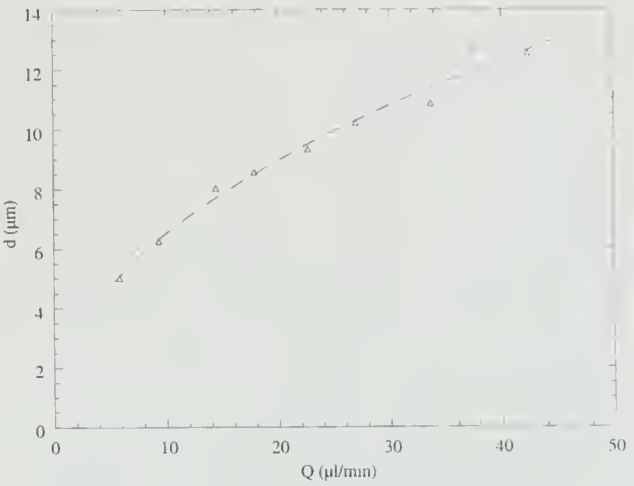


Fig. 8. Electrospray droplet diameter (d) versus liquid flow rate (Q) for deionized water at constant applied voltage. (From Reference 5, with permission.)

with which charge in the liquid interior relaxes to the surface. There appears to be no consensus on the functional form of $f(\epsilon)$ appearing in Equation 1.[19] This relationship is not considered in detail, since it is not critical to the intended purpose of this review. It is apparent from Equation 2 that, for a given electrosprayable solution, droplet size can be selected by varying the liquid flow issued from a single capillary. As an example, Figure 8 shows the dependence of the droplet size on liquid flow for a fixed electrode configuration for deionized water.[5] For flow rates ranging from 5.8 to 42.4 $\mu$L/min the droplet diameter varies from 5 $\mu$m to about 12 $\mu$m. Stability problems of the spray at flow lower than 5.8 $\mu$L/min prevented the generation of smaller droplets.

Since saline solution is a commonly used liquid excipient in drug administration, electrosprays of water with various concentrations of NaCl were also investigated experimentally. Experiments showed that a stable spray could be established in the droplet size range relevant to targeted inhalation when the NaCl concentration was $\leq 0.005\%$ by weight. Figure 9 shows results for the aqueous saline solution of 0.005% NaCl by weight, for various voltages and flow rates.[6] The maximum flow in the cone-jet mode was about 10 $\mu$L/min, and the corresponding droplet diameter was 2 $\mu$m. Lower concentrations of NaCl can be used to bridge the diameter gap between 2 $\mu$m and the smallest diameter obtained for deionized water, 5 $\mu$m. Compared with pure water spray, the spray of saline solution, with a measured electric conductivity of the solution 2 orders of magnitude larger than deionized water, yielded smaller droplets at constant liquid flow, which confirmed the qualitative observations of Smith.[20] Thus, for aqueous solutions, control of salinity, and therefore conductivity, may offer another degree of control over droplet size.

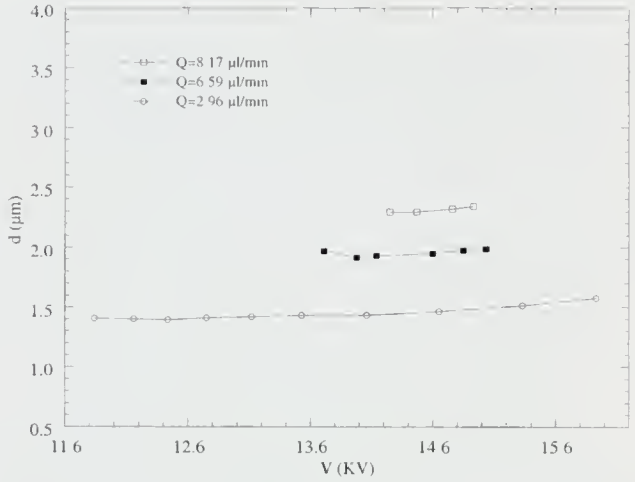


Fig. 9. Electrospray droplet diameter (d) versus applied voltage (V) at 3 liquid flow rates for a solution of water and 0.005% NaCl. (From Reference 6, with permission.)

The data in Figure 9 indicate that at a given flow and for a specific electrode configuration the electrospray can be operated only within a finite range of voltages. Below the lower voltage limit the electrospray pulsates with a discontinuous emission of mass from the liquid meniscus. Above the higher voltage limit other instabilities arise that result in either wild whipping of the jet or in the formation of several uncontrolled jets. In both cases the droplet size distribution broadens drastically. Between those 2 limits there is a reasonably wide range of voltages within which a stable, monodisperse spray can be established in the cone-jet mode. By searching for the voltage limits at different flow rates, one can construct a stability domain for proper operation. Figure 10 shows such a domain for the deionized water data of Figure 8.[5]

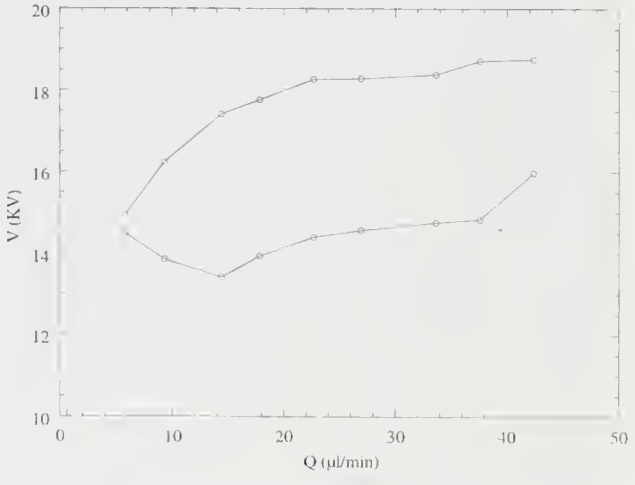


Fig. 10. Electrospray cone-jet mode stability domain for deionized water: voltage (V) versus liquid flow rate (Q) for a fixed electrode configuration. (From Reference 5, with permission.)

Notice that the value of the applied voltage is not particularly relevant. The establishment of the cone-jet mode depends on the intensity of the electric field affecting the stress applied to the fluid to overcome the surface tension and extrude the liquid ligament. Different electrode configurations require different voltages for the establishment of a given field. As a result the curves in Figure 10 can shift either up or down substantially. Typically, the operational range of the electrospray covers several hundred volts and falls in the range of 1–15 kV, depending on electrode geometry, surface smoothness, and material electric properties.

In Figure 10 notice that in principle there are 2 more bounds to the operating envelope of the electrospray: an upper liquid flow limit* and a lower one. Most of the emphasis in the scaling studies[17–19] has been on the production of very small droplets. Not much was reported on the upper flow limit, except for the report by Chen and Pui,[19] in which it was observed that $k \times Q_{max}$ is approximately constant, a result that can be explained in terms of competing characteristic lengths. Increasing the liquid conductivity thus decreases the typical flow rates that can be stably sprayed,[8] which also results in smaller droplets, as the data in Figure 9 suggest.

A few relationships have also been offered for the minimum liquid flow, but they seem to be in modest agreement with experimental findings, at least for a broad range of dielectric constants.[19] At least for an order-of-magnitude estimate one can use

$$Q_{min} = (\varepsilon\varepsilon_0\gamma)/(\rho_p\kappa) \qquad (3)$$

with the same notation of Equation 2 and with $\rho_p$ denoting the liquid density, as suggested by de la Mora and Loscertales.[17]

Liquid viscosity intervenes by affecting the relationship of droplet size and liquid jet diameter, through the dominant instability mode that leads to break-up. However, with typical liquids of relevance to inhalation therapy, such as water and light alcohols, the role of viscosity is negligible.[17]

The liquid surface tension does not appear in the scaling laws above and does not affect the size of the generated droplets. However, it may affect the sprayability of solutions with high surface tension. In fact, for a fixed electrode configuration and liquid flow, the voltage necessary

* It should be also pointed out that the largest flow presented in Figure 11 does not represent an upper limit for stable spray operation. Electrosprays beyond that range were not examined because they would generate droplets too large for inhalation applications. Nevertheless, at least for more conductive fluids, one may be constrained by such a limit.

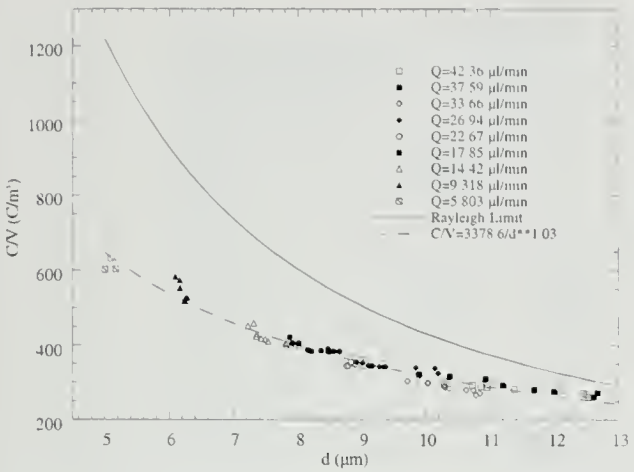


Fig. 11. Average droplet volume charge density (C/V) versus average droplet diameter (d) for various flow rates of deionized water. The solid line is the Rayleigh limit. The dashed line correlating the data points has a diameter dependence as $d^{-1}$. (From Reference 5, with permission.)

to operate a stable spray scales with the square root of the surface tension.[20] If the surface tension is sufficiently large, as in the case of water, the necessary voltage may be higher than the electric breakdown threshold of the surrounding gas medium (usually air), and corona discharge would ensue. This phenomenon typically destabilizes the electrospray behavior and results in fairly broad size distributions unsuitable for targeted drug delivery.[21–23]* A natural way to tackle this problem is to use a sheath gas that has a relatively high electric breakdown threshold, to prevent or delay the onset of corona discharge. A similar approach proved effective, for example, in electrospray ionization.[25] The water data in Figures 5, 6, and 8–11 were obtained using carbon dioxide as sheath gas. At the typical flow of inhalation studies, on the order of 10 L/min, a molar carbon dioxide concentration of $< 0.5\%$ is sufficient for the establishment of a water electrospray. Such a carbon dioxide level is sufficiently low to cause no problems, even in the treatment of asthmatic patients. Alternatively, if the addition of a sheath gas is too cumbersome, especially for portable inhalation devices, the water surface tension can be reduced by adding suitable surfactants, which is the approach pursued by BattellePharma.

### Electric Charge: Consequences and the Need to Neutralize the Droplets

The dispersion of a liquid by electrostatic means offers, in addition to size control, another distinct advantage over other nebulization techniques. Because of the presence of net charge on the surface of the generated droplets, the Coulombic repulsion among droplets prevents droplet agglomeration and aids spray penetration in the host gas by causing droplet self-dispersion. For a droplet undergoing evaporation, the evaporation results solely in mass loss, while the charge remains attached to the droplet,[26] so the charge density (charge per unit surface area) increases until a critical condition at which the droplet becomes unstable and emits "offspring." This phenomenon occurs near the so-called Rayleigh limit, when the repulsive force of electrical charges of the same polarity overcomes the surface tension cohesive force holding the droplet together. Under evaporative conditions, which may be encountered in drug inhalation, droplet fission may be inevitable unless efforts are made to discharge the droplet. It is then relevant to examine the level of charging that the electrospray can produce and compare it to that theoretical limit.

To this end, the average charge level has been determined experimentally by measuring the total current collected by the ground electrode. Since an electrospray operating in cone-jet mode generates a very narrow size distribution, the volume charge density of the electrospray can be well represented by a mean value calculated from the ratio between the total electric current and the total liquid flow. In Figure 11 such an average droplet charge density for deionized water sprays is plotted as a function of the average droplet diameter, the latter measured close to the spray origin to minimize possible evaporation effects.[5] The solid line in the figure is the calculated Rayleigh limit, which is the stability limit for the charged droplet, given by:

$$q^2 = 8\pi^2\varepsilon_0\gamma D^3 \qquad (4)$$

in which $q$ is droplet charge at the Rayleigh limit,[27] $\epsilon_0$ is the permittivity of the medium surrounding the droplet, $\gamma$ is the liquid surface tension, and $D$ is the droplet diameter. Figure 11 shows the charge density to be a decreasing function of droplet size. The large droplets with lower charge density are closer to the Rayleigh limit and thus are more likely to become unstable. As also found in other studies,[8,28] the droplet charge density is *not* a constant fraction of the Rayleigh limit, in contrast with the predictions of models that have from time to time surfaced in the literature.[29,30] Figure 11 also shows that for all the liquid flows tested, from 5.8 up to 42.4 µL/min, the data are well-correlated by a least squares fit curve, according to which the volume charge density varies with the inverse of the droplet diameter. This dependence suggests that these electrosprays are established at approximately constant surface charge density, and since the latter is proportional to the electric field, regardless of the particular geometry, at constant electric field.

* Under special circumstances a weak corona has been reported to have a stabilizing effect on the spray[8] and may enhance the flexibility of the electrospray system to generate droplets of a given size.[24]

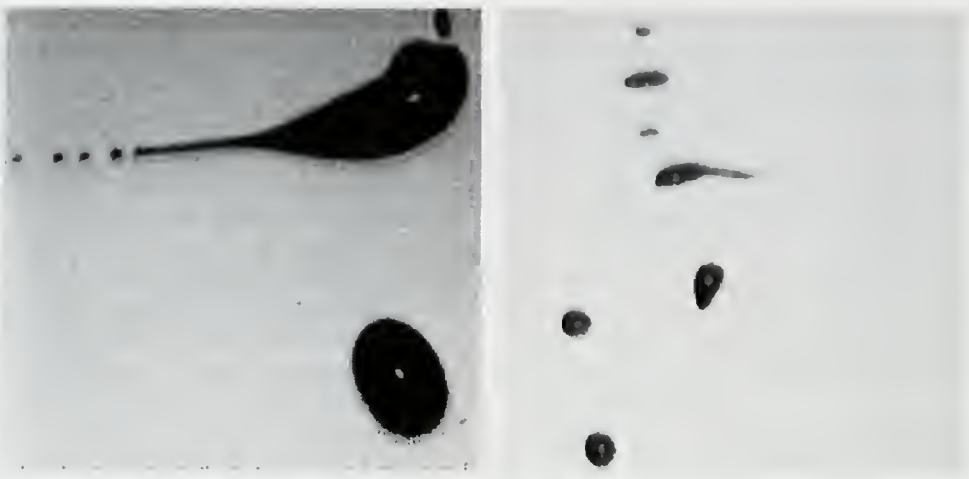

Fig. 12. Examples of Coulombic fission of droplets near the Rayleigh limit. (From Reference 28, with permission.)

Figure 12 shows examples of droplet fission, resulting in the formation of cones that emit droplet offspring.[28] (Notice that photographing the droplet fission event with an optical microscope and obtaining some spatial resolution required relatively large droplets of liquid hydrocarbons.) Typically the droplet fission phenomenon is encountered at charge levels on the order of 80% of the Rayleigh limit. Clearly this phenomenon would affect droplet size distribution and the targetable area for lung deposition.

Because the respiratory tract is virtually grounded, charged droplets would deposit predominantly in the upper respiratory tract under the action of image forces,[2] even if the droplets' inertial behavior would otherwise enable deep lung penetration. Discharging the droplets is therefore necessary to prevent oropharyngeal deposition, and an electrospray aerosol delivery system must include a controlled means to discharge the droplets. Figure 13 shows the simplest discharge system.[5] Discharging is performed after the droplets have dispersed, to prevent droplet coalescence near the liquid meniscus, where the droplet concentration is highest. The spray is generated between the capillary tube and a metal porous disk. The tube is shielded by a carbon dioxide sheath flow for the reasons discussed above. Both the tube and the porous metal disk are maintained at independently controlled potentials. A 2 mm hole at the center of the porous disk allows the charged droplets to pass through the disk. The inertia of the droplets traveling at high velocity near the electrospray source overcomes electrostatic attraction between the droplets and the disk and prevents their interception by the disk. Farther downstream of the porous metal disk a ground discharge needle is placed in the axis of the delivery system, at a distance of approximately 40 mm from the porous disk. The intensity of the discharge can be controlled by changing the potential difference between the porous

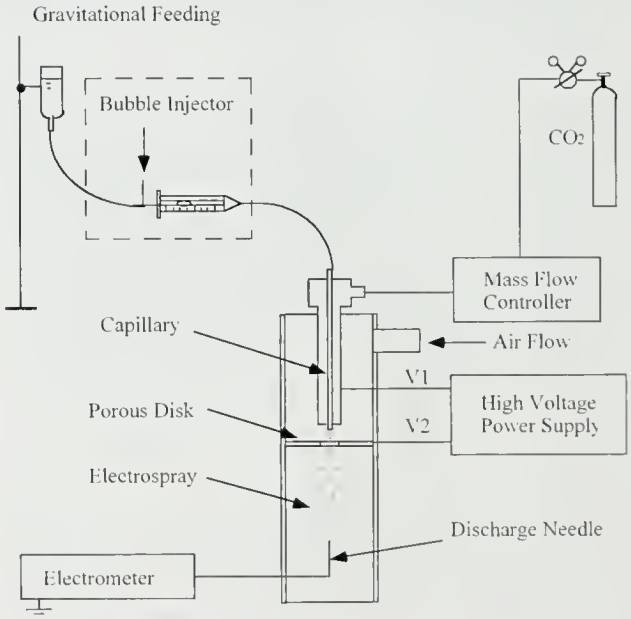


Fig. 13. Prototype of electrospray monodisperse aerosol delivery system, including droplet discharging system. V = voltage.

disk and the discharge needle, while the potential difference between the tube and the porous disk is kept constant to preserve the spray stability. The discharged spray is finally delivered into a tube by a coaxial air flow.

This droplet charge neutralization scheme is similar to that implemented originally by Noakes et al[31] and recently used by Meesters et al.[21] In preliminary experiments a metal plate was positioned under the discharge needle and insulated from it. The plate was connected to an electrometer. By varying the voltages between the porous disk and the discharge needle, the effectiveness of the corona in discharging the spray was monitored by measuring the current on the plate with and without the electrospray. The

difference between those 2 current signals represents the net current carried by the electrospray in the presence of the discharge. Experiments showed that by adjusting the applied voltage between the porous disk and the needle, the discharge current can be controlled and therefore the electrospray can be discharged either partially or completely. The spray was observed under white light illumination. In the case of complete neutralization of the droplet charge, the droplets, instead of following well-defined trajectories partially determined by the external electric field, became tracers of the gas co-flow and followed convoluted trajectories because of the turbulence of the host co-flow. It should be mentioned that for the typical current levels of these water sprays, on the order of $\leq$ 100 nanoamperes, the corona current generated for neutralization should yield ozone concentration small enough to pose no health hazards.[32]

### The Need for Multiplexing

The goal of delivering a certain liquid flow in droplets of the optimal deposition size may not be achieved with independent control of these 2 variables, because they are related to each other through some liquid physical properties, as shown in Equation 2. The implication of Equation 2 is that if drug deposition requires a particular droplet size (D) and if the liquid solution in which the drug is dissolved or suspended is fixed (ie, for fixed $\epsilon$ and k), the flow required by the therapeutic objective and the patient's tolerance for the duration of aerosol inhalation may not be achievable from a single electrospray cone-jet source, so *multiplexing* is required. Indeed, the data in Figure 9 suggest that the aerosol production from a single cone-jet source is inadequate for inhalation therapy. Multiplexing is necessary in most cases, even accounting for the anticipated improvement in respirable dose efficiency and the resulting lower aerosol flow rate needed for a given therapy. Multiplexing entails replacing the single electrospray capillary tube with a matrix of closely spaced tubes, each with its own cone-jet mode spray.

Multiplexing has become easier to achieve, even at large scales, with recent progress in the field of microelectromechanical systems. Namely, by adapting the integrated circuit lithographic technology of the electronic industry to chemical and mechanical engineering applications, multiplexing can be achieved at unparalleled scales and with submicron precision. Figure 14 shows an example of the protrusions that can act as individual electrospray nozzles operated in parallel. The figure shows 3 views of a multiplexed electrospray distributor realized in silicon by deep reactive ion etching. Although the technique at this prototype stage is very expensive, it lends itself to mass production economies of scale, which has been a key factor in the extraordinary growth of the electronics industry in the last few decades.

Fig. 14. Multiplexed electrospray distributor manufactured with a deep reactive ion etching microfabrication technique. (Courtesy of Xiaohui Li, James Klemic, and Mark Reed, Yale University, personal communication, 2002.)

### The BattellePharma Electrospray Nebulizers

Electrospray entails providing a regulated voltage supply and some suitable means to pump the liquid at a controlled flow rate. In view of the small electric currents involved, an electrospray can be battery-operated, as is the case with the portable BattellePharma inhaler in Figure 1. The small current also means the device poses no health hazard, despite the high voltage, even if improperly used. Developments at BattellePharma aimed at miniaturizing the power supply and the piezoelectric pumping system have been very successful, as the scale of the device in Figure 1 suggests.

No thermal degradation of the aerosolized substance is anticipated, and the experience of the mass-spectrometry community with electrospray ionization has shown that the technique is sufficiently "soft" to cause no fragmentation, even of labile proteins and peptides. This is one of the reasons the electrospray is becoming the preferred choice to inject large, ionized macromolecules into a mass spectrometer for chemical analysis.[33] In the case of insulin, which is being considered for inhalation treatment of diabetes, no loss of biological activity was found in vitro for nanopowder produced by electrospray drying.[34]

A potential limitation to the biomedical use of electrospray is the constraint on the conductivity of the solution to be electrosprayed, as indicated by the experiments with NaCl/water solutions. Some solutions in which pharmaceutical substances are typically dissolved and stabilized may prove too conductive for direct electrospraying in the target droplet size range. In that case, however, a variation of the sheath technique can be tried, with a sheath flow of a *liquid* with physical properties appropriate for good electrospray performance, as has been done in electrospray ionization for high ionic strength buffers.[35]

Swift emphasizes the need for a "low-volume, once-through aerosol generation," in which small volumes can be charged to the device and be completely aerosolized over a specified time interval.[3] Applications in which expensive substances are used for either diagnostic or research purposes (eg, gene transfer therapy) will require more efficient systems in which very small amounts can be aerosolized with minimal losses. The electrospray is an ideal device for this purpose, since it can continuously aerosolize very small charges of liquid.[36]

The droplet size can be selected to promote deposition in either central or deep lungs, as required by the therapeutic goal. Since electrospray capillary tubes have large inner diameters, even suspensions can be successfully sprayed.

Although the physical principles discussed so far hold true also for the BattellePharma inhalers, the adaptation of the electrospray to the BattellePharma devices is quite different from the schematics shown in Figures 2 and 13.[37] BattellePharma inhalers have 17 multiplexed electrosprays at negative potential and the corona at positive potential. The fabrication technique involves injection molding, by which the electrospray source is molded in a nonconducting material and the charge is injected into the drug solution by a metal electrode in the solution reservoir. The discharging surfaces are manufactured from stamped sheet metal. As a result of these simplifications it appears that fabrication of an electrospray-based nebulizer can be economically competitive with other types of nebulizers. The maximum flow rate of the BattellePharma device is in the range of 8–16 $\mu$L/s, which is suitable for practical inhalation therapy. The device is user-friendly, can be breath-activated, and includes a dose counter. BattellePharma experience has focused primarily on ethanol-based formulations, because they are easy to electrospray. But, as discussed above, aqueous solutions with either a carbon dioxide sheath gas or a surfactant can be successfully nebulized with this technique. A Phase I clinical trial with human volunteers and in vitro studies showed dramatically better respirable dose efficiency (by a factor of at least 2 or 3) than commercial metered-dose inhalers or dry powder inhalers (up to 78%).[37*]

#### ACKNOWLEDGEMENTS

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### Discussion

**MacIntyre:** How do you put the charge on the drug? What do you do to it so that it can pass through this system and nebulize?

**Gomez:** I don't think you actually charge the *drug*; you charge the liquid carrier in which the drug is dissolved or suspended, in the cone on the capillary tube from which the spray issues. At the source of the electrospraying you have separation of the ions in the solution. So, for example, if you apply a positive potential, you wind up with negative ions being neutralized at the high voltage electrode, and you wind up with overall charged liquid of the same polarity. The liquid is dispersed in charged droplets, which are neutralized by the corona discharge before the solvent evaporates. So it is unlikely that there is any charge left on the drug itself, except for what may be naturally present when the drug is put in solution.

**MacIntyre:** So the drug starts with no charge.

**Gomez:** Right. No additional charge from the electrospray process.

**MacIntyre:** Right out of the bottle. And it's charged inside the capillary tube and then gets sprayed.

**Gomez:** Right. But it's *not* the drug, it's the carrier that's charged.

**MacIntyre:** I'm trying to picture if the Food and Drug Administration or somebody is going to have a problem with this. Are these drugs safe to put these charges on and to discharge? You seem to imply that it's OK.

**Gomez:** I have absolutely no doubt, because what we care about is denaturation or fragmentation of the drug, and there is robust evidence from mass

spectrometry that electrospray is a sufficiently soft ionization technique that it does not damage the drug.

**Smaldone:** I think ultrasonic nebulizers produce charged particles too, but by the time they get out of the device they've become neutral. So you *could* argue that the predicate devices also produce charged particles; that's one way of addressing Food and Drug Administration concerns. Can you give us some idea of the mass of delivery? One of the advantages of nebulizers is that they can deliver milligrams of drug. How much drug can an electrospray deliver?

**Gomez:** I think the largest flow rate that BattellePharma has is on the order of 1 mL/min. But it's slightly larger. Alex, do you want to comment on this?

**Stenzler:*** BattellePharma has pumped it up to 30 $\mu$L/s.

**Gomez:** Which is about 1.8 mL/min.

**Smaldone:** That's comparable to a nebulizer.

**Gomez:** Yes. Because of the constraints that I indicated, the way they do it is with a multiplexed system of several capillary tubes.

**Dolovich:** You said that you're getting rid of the smaller, satellite droplets. I wonder what size those satellite droplets are and whether they might be clinically useful?

**Gomez:** Actually, you don't always get satellite droplets, because it all depends on the volatility of the liquid being nebulized. In some cases you don't see such a distinct difference between the primary or core droplets and the satellites. It turns out that the satellites account for only 5–6% of the total. You don't necessarily get rid of them. But because they are smaller, as small as a third of the primary droplet size, they evaporate relatively fast, so ultimately a small percentage of the stuff may go into very tiny droplets that eventually have fully evaporated. They don't substantially affect your deposition goals. I didn't deliberately get rid of them; it's nature that does it for us: because the satellite droplets' charge-per-volume is higher, they are much more "responsive," if you will, to the electrostatic field that is imposed, as opposed to the slightly more sluggish, more inertia-driven, larger droplets.

The second factor is also inertia-related. The satellites are smaller, so they move out a little faster because of the electrostatic repulsion. So it's a natural separation that takes place. But I wouldn't pay too much attention to this. The example I showed was of large droplets (10–40 $\mu$m) of heptane. If you spray water in 2–3 $\mu$m droplets you don't see that sharp distinction between the primary and satellite droplets.

**Geller:** A lot of devices are "open" devices, meaning they can accommodate whatever you put into them. But it seems that if the various liquids have different electrical permittivities, conductivities, and viscosities, then each drug might require a device made specifically for that fluid.

**Gomez:** I don't think so. In principle, as you change liquid physical properties, the optimal flow rate to produce 3-$\mu$m droplets might shift, but this might only affect the level of multiplexing that you want to achieve. Since multiplexing can be done fairly easily, they would probably have different levels of multiplexing, depending on how different are the liquid properties. I'm not sure that's the way they intend to operate, but, again, I've shown you only the purest form of electrostatic sprays. You can be a little more forgiving. They seem to be accepting somewhat broader sizes to be issued, and still do exceedingly well.

**Fiel:*** What about environmental contamination? Is release of aerosol into the ambient air decreased because of the way the particles are created by electrospray?

**Gomez:** The portable device I've seen is breath-actuated, and I presume the stationary device is also breath-actuated.

**Barry:** There was some work by Hashish and Bailey about 10 years ago that suggested that charging particles would improve lung deposition of nebulizer aerosol[1,2] and that the charge itself had a therapeutic benefit. Do you think there's an applicability to using the charge as a part of the therapy?

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**Gomez:** I don't know much about the physiologic effect of charge, but for all intents and purposes, the walls of the respiratory tract are "grounded." I would suspect that you will get very little deposition in the deep lung unless you discharge the droplets. Maybe charge has a beneficial effect, but the question is how to get the drop-

* Alex Stenzler RPFT, VIASYS Healthcare, Yorba Linda, California.

* Stanley B Fiel MD, MCP Hahnemann University, Philadelphia, Pennsylvania (discussant for Monaghan Trudell, Syracuse, New York).

lets into the lung? Maybe if you had a catheter or other intrusive technique to deliver the droplets directly into the lung, then charge may even be useful. In that case you can have Coulombic explosion—the fission that would cause deposition onto the walls. But if you plan to inhale the aerosol through the mouth, there's no doubt that the droplets will be intercepted in the upper respiratory tract unless they are discharged.

Schofield's Inhaler from *The American Armamentarium Chirurgicum*
New York: George Tiemann & Co. 1879
Courtesy of Health Sciences Libraries, University of Washington

# Smart Nebulizers

Gerald C Smaldone MD PhD

**Introduction**
**Principles**
**Oropharyngeal Deposition**
**Deposition in the Deep Lung**
**Variability in Particle Deposition**
**Smart Nebulizers**
**Breath Actuation**
**Control of Dose During Tidal Breathing (Adaptive Aerosol Delivery)**
**"Slow and Deep" Aerosol Delivery Systems**
**Summary**

**Physicians are familiar with conventional nebulizers, which deliver aerosols in a relatively uncontrolled manner. As aerosol medications evolve beyond bronchodilators, the need for control of dose variability, the possibility of overdose, and the need for efficient delivery have provoked the industry to redesign aerosol delivery systems. The need to target aerosol delivery to specific lung regions has focused efforts to coordinate aerosol delivery with defined breathing maneuvers. This review summarizes the major factors affecting aerosol deposition, discusses how those factors are guiding new designs for aerosol delivery systems, and describes some examples of the improved precision and efficiency of those systems.** *Key words: nebulization, nebulizer, aerosol, lung deposition.* [Respir Care 2002;47(12):1434–1441]

## Introduction

As aerosol delivery systems, nebulizers typically deliver aerosols continuously while the patient breathes tidally. Advances in aerosol device development involve both changes to aerosol-generating technology and a direct interaction between the device and the patient. To understand this interaction it is useful to review the basic factors that affect the clinical delivery and deposition of aerosols. This review focuses on physiologic factors that affect deposition and how those factors have been incorporated into "smarter" aerosol delivery systems.

Gerald C Smaldone MD PhD is affiliated with the Pulmonary/Critical Care Medicine Department, State University of New York at Stony Brook, Stony Brook, New York.

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Correspondence: Gerald C Smaldone MD PhD, Pulmonary/Critical Care Medicine, Health Sciences Center, T-17–040, State University of New York at Stony Brook, Stony Brook NY 11794-8172. E-mail: gerald.smaldone@stonybrook.edu.

## Principles

### Oropharyngeal Deposition

As particles are inhaled, they must negotiate the oropharynx. For the treatment of certain diseases (eg, croup) oropharyngeal deposition can be useful. For diseases of the deep lung the oropharynx is a barrier to drug delivery.

Particle inertia influences the degree of oropharyngeal deposition. The "ballistic" qualities of an aerosol are defined by the mass and velocity of the aerosol particles and by local airway geometry. There is a direct interaction between velocity and airway geometry, because changes

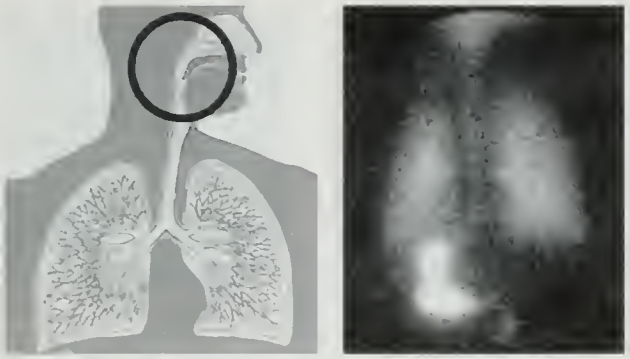

Fig. 1. Left: Oropharynx (circled) and the other airways. Right: Deposition pattern of nebulized Pulmozyme in a 9-year-old child. Approximately 60% of the deposition was to the stomach, representing oropharyngeal deposition, which is influenced by the mass and velocity of the aerosol particles and by airway geometry. (From Reference 2, with permission.)

in local airway cross section affect linear velocities. These factors are quantitatively related by the Stokes number, which is calculated by the simplified Stokes equation:

$$\tau U/d$$

in which $\tau$ is the mass component of the particle (which includes the square of the particle diameter), U is the local particle velocity, and d is the local airway geometry. Thus, the larger the particle ($\tau$), the faster it is moving (U), and the narrower the local airway diameter (d), the greater the inertia of the particle.

With nebulizers, which generally produce low-velocity aerosols,[1] the patient's breathing pattern determines the

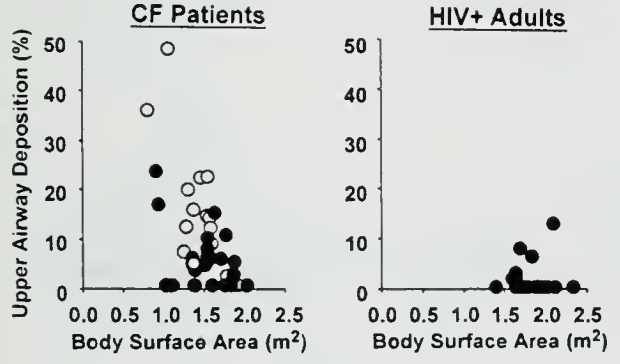


Fig. 2. Upper airway deposition in cystic fibrosis (CF) patients (left) and in adults with human immunodeficiency virus (HIV+). The CF patients inhaled 1.1 $\mu$m particles (closed circles) and 3.0 $\mu$m particles (open circles). For both aerosols there appears to be considerable overlap when upper airway deposition is plotted against body surface area. This suggests a geometric factor that changes as a person grows. For the adults, upper airway deposition was negligible (1.1 $\mu$m, $n$ = 26). (From Reference 3, with permission.)

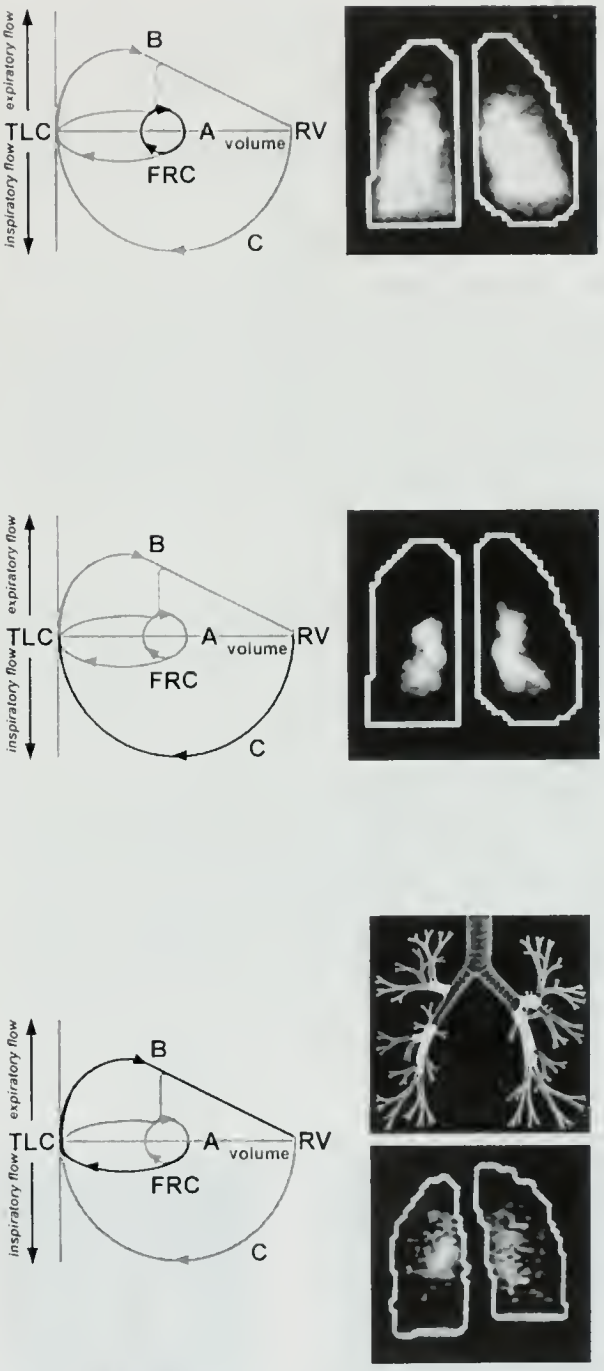


Fig. 3. The relationship of lung deposition to breathing pattern. The flow-volume loops (in which flow is on the vertical axis and lung volume is on the horizontal axis) correspond to the adjacent lung deposition images. Breathing pattern is indicated by the darkened flow-volume path. Upper panel: Deposition during quiet tidal breathing. Middle panel: Deposition during forced inspiration. Lower panel: Deposition during tidal inspiration and forced expiration; the sites of flow limitation shown in the sketch of the tracheobronchial tree correspond to sites of deposition in the deposition image. TLC = total lung capacity. RV = residual volume. FRC = functional residual capacity. See text for discussion of terms A, B, and C.

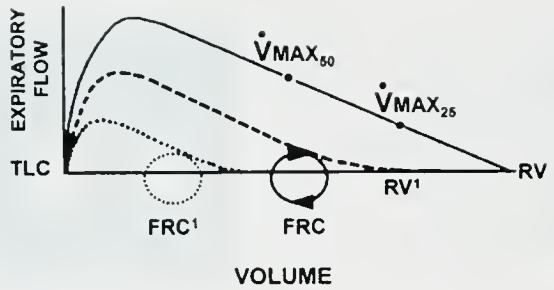


Fig. 4. Maximum expiratory flow-volume curve for a normal subject (solid line), a subject with moderate obstructive disease (dashed line), and a subject with severe obstructive lung disease (dotted line). For the obstructed patients the tidal loop is superimposed on the maximum expiratory flow-volume curve. The obstruction increases functional residual capacity (FRC), and as the disease process worsens, residual volume (RV) also increases. $\dot{V}_{max50}$ = instantaneous forced expiratory flow when the lung is at 50% of vital capacity. (From Reference 8, modified with permission.)

velocity (U). Therefore, all other things being equal, the best way to maximize the passage of aerosol particles through the oropharynx is to inhale slowly and have the particles be as small as possible ("small and slow"). Despite textbook predictions, particles within the so-called "respirable range" (1–5 $\mu$m) can deposit in the oropharynx of a child, even during tidal breathing. Figure 1 shows a scan of a 9-year-old child who inhaled a radiolabeled aerosol (of Pulmozyme) that had a mass median aerodynamic diameter of 3.0 $\mu$m. Approximately 60% of the aerosol appears in the stomach, meaning that it had first deposited in the oropharynx.[2] Figure 2 shows upper airway deposition data in adults and children. The figure shows that upper airway deposition is higher for both 1 $\mu$m and 3 $\mu$m particles in younger children (who have lower body surface area), whereas those particle sizes do not deposit in the oropharynx in adults.[3] That suggests that airway geometry can be the dominant deposition factor in younger children, despite relatively small particles (as small as 1.0 $\mu$m) and typical patterns of tidal breathing.

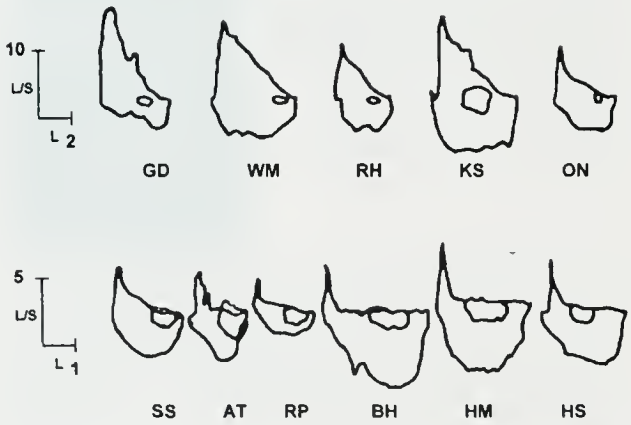


Fig. 5. Maximal flow-volume loops superimposed over tidal breathing loops from normal subjects (upper row) and patients with severe obstructive lung disease (lower row). Note the difference in the sensitivity of the flow axis (10 L/s with the normals; 5 L/s with the obstructed patients). (From Reference 9, modified with permission.)

Fig. 6. Left: Flow-limiting segments in the tracheobronchial tree (white segments in left panel). Right: Corresponding lung deposition image (posterior view) from a patient with severe chronic obstructive pulmonary disease. Particle deposition occurs at flow-limiting segments. (From Reference 10, with permission.)

### Deposition in the Deep Lung

The patient's breathing pattern is the most important factor affecting deposition to the deep lung. Figure 3 illustrates the relationship of breathing pattern and deposition in adults. To summarize as much physiology as possible, I have chosen to relate deposition to the position of the subject's breathing pattern on the flow-volume relationship of the lung. The axes depicted in Figure 3 are flow (vertical axis) and lung volume (horizontal axis). Breathing begins at functional residual capacity (FRC) and the tidal loop is outlined in the upper panel. Tidal breathing is initiated at point A: inspiratory flow is downwards and volume increases to the left. The loop is closed during expiration. The right-hand panels show the corresponding lung deposition patterns. Lung outlines were determined

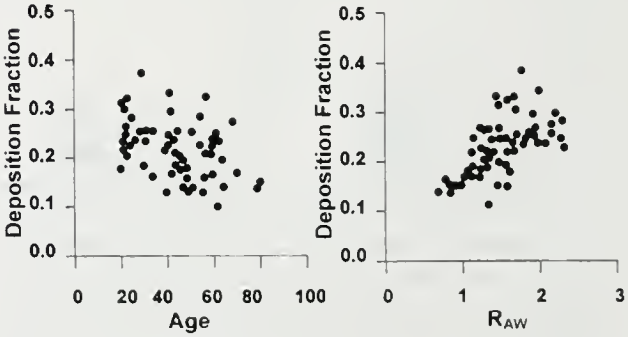


Fig. 7. Variability in deposition during tidal breathing: deposition fraction (DF) versus age (left panel) and airways resistance ($R_{AW}$). There appears to be a correlation for both relationships, but it is stronger for airway resistance. (From Reference 12, with permission.)

Table 1. Variability of Fine Particle Deposition in Healthy Adults: Effect of Age and Sex

| | Male ($n$ = 25) | Female ($n$ = 37) | p |
|---|---|---|---|
| Deposition fraction | 0.24 ± 0.05 | 0.28 ± 0.06 | 0.007 |
| Pulmonary function ($R_{AW}$) | 0.80 ± 0.32 | 1.32 ± 0.43 | < 0.001 |

Values are mean ± SD
$R_{AW}$ = airway resistance.
(Adapted from Reference 12.)

by equilibrium xenon scan. In the upper panel, particle deposition appears to be relatively peripheral and primarily in the lower lung regions. This pattern reflects the concept of increased ventilation in the lower lobes during tidal breathing near FRC. The subject in Figure 3 had inhaled a monodisperse aerosol of 1.5 $\mu$m particles, and deposition in the oropharynx and central airways was negligible.

The middle panel of Figure 3 shows a markedly different pattern of inspiration, with the subject inhaling as rapidly as possible along the maximal inspiratory flow-volume relationship (curve C, expiration is not shown). With this breathing pattern, particles deposit in central airways, at bifurcations, and inspiratory impaction is the dominant force affecting deposition. Even at these rapid flows, in adults small particles can make it through the oropharynx, as shown in the deposition image.

The lower panel in Figure 3 represents an interesting pattern of breathing and deposition: the subject inhales slowly from FRC to total lung capacity and immediately performs a maximal expiratory flow-volume maneuver (curve B) from total lung capacity to residual volume. During a forced expiration the central airways collapse and form flow-limiting segments,[4] which tend to form in

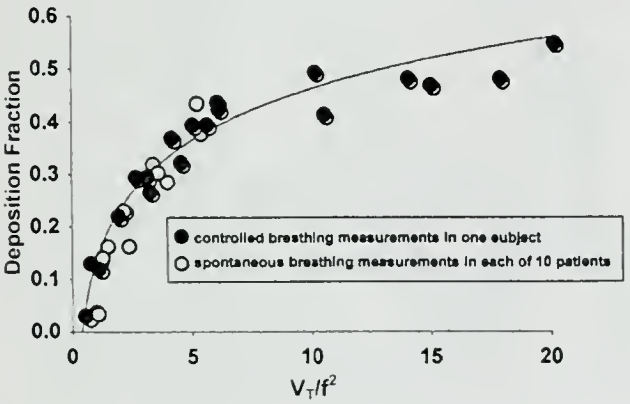


Fig. 8. Deposition fraction (DF) versus pattern of breathing defined by a relationship that represents a measure of the period of breathing (tidal volume divided by breathing frequency squared [$V_T/f^2$]). Data for controlled breathing in a single subject are superimposed on measurements obtained from spontaneously breathing patients. (From Reference 13, with permission.)

Table 2. Air Flow and Particle Deposition in Normals Versus Patients with Severe Obstructive Lung Disease

| | $FEV_1$ (% of predicted) | C/P Tidal | DF Tidal |
|---|---|---|---|
| Normal subject 1 | 78 | 1.10 | 0.08 |
| Normal subject 2 | 77 | 1.06 | 0.04 |
| Normal subject 3 | 74 | 1.06 | 0.51 |
| Normal subject 4 | 71 | 0.94 | 0.25 |
| Normal subject 5 | 62 | 1.02 | 0.04 |
| Mean ± SD | | 1.02 ± 0.73 | 0.18 ± 2.01 |
| r | | 0.351 | 0.132 |
| | | p = NS | p = NS |
| Flow-limited subject 1 | 38 | 1.81 | 0.31 |
| Flow-limited subject 2 | 34 | 2.37 | 0.41 |
| Flow-limited subject 3 | 31 | 1.69 | 0.54 |
| Flow-limited subject 4 | 21 | 2.46 | 0.29 |
| Flow-limited subject 5 | 14 | 0.92 | 0.16 |
| Mean ± SD | | 1.85 ± 0.13 | 0.34 ± 0.13 |
| r | | 0.636 | 0.871 |
| | | p = NS | p < 0.05 |

C/P = ratio of central deposition to peripheral deposition.
DF = deposition fraction.
NS = not significant.
(Adapted from Reference 11.)

lobar and segmental bronchi (highlighted in the tracheobronchial tree in Figure 3).[5] These dynamic resistors limit flow and create zones of high turbulence and particle acceleration, which affects the deposition of particles being exhaled from the deep lung.[6] Deposition during flow limitation is enhanced, as shown in Figure 3, as particles have

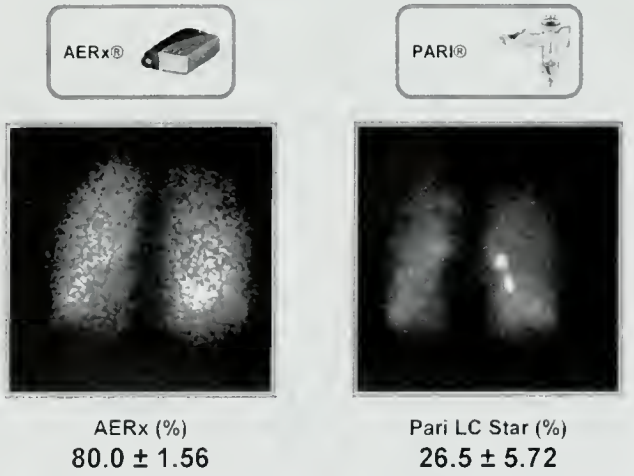


Fig. 9. Deposition images from an asthmatic patient, obtained during different patterns of breathing: single inspiration with the AERx (left) and tidal breathing with the PARI nebulizer (right). Mean ± standard deviation deposition fractions from 4 asthmatic subjects were: AERx 80.0 ± 1.56%; PARI 26.5 ± 5.72%. Variability is much greater with the PARI device (tidal breathing) than with the $AER_x$ (single breath). (From Reference 14, with permission.)

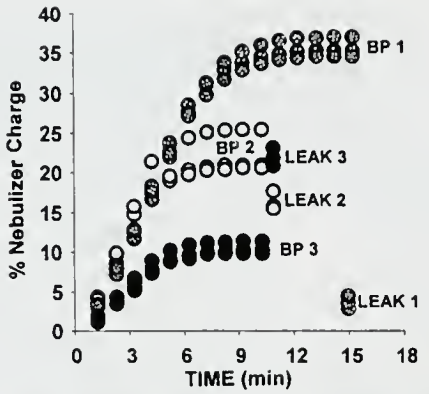


Fig. 10. Inhaled mass as percentage of nebulizer charge versus time for the AeroEclipse nebulizer. Data points are shown for breath actuation (tidal volume 440 mL) and continuous nebulization (tidal volume 200 and 50 mL). Breathing pattern 1 (BP1, stippled circles): $V_T$ = 440 mL, respiratory rate (f) = 19 breaths/min, duty cycle (ratio of the inspiratory time to the total breathing cycle time) = 0.5. Breathing pattern 2 (BP2, open circles): $V_T$ = 200 mL, f = 25 breaths/min, duty cycle = 0.5. Breathing pattern 3 (BP3, closed circles): $V_T$ = 50 mL, f = 40 breaths/min, duty cycle = 0.5. Aerosol released into the environment (leak) is also shown. (Adapted from Reference 15.)

deposited in central lung regions in a normal subject during a forced expiration.[7]

Figure 4 is another representation of the maximal flow-volume relationship, but with only events during expiration and tidal breathing depicted. The normal curve is shown with the representative maximum flows at 50% and 25% of vital capacity (VC). The 2 flow-volume relationships below normal represent moderate and severe obstructive lung disease. For example, as a patient develops emphysema and there is loss of elastic recoil, maximum expiratory flow diminishes.[8] With moderate disease, maximum flow can be superimposed on tidal breathing, as illustrated by the superimposition of the 2 curves near the normal tidal loop. Over time, as the disease progresses, maximum flow can reduce even further. To sustain tidal breathing at normal levels, FRC must increase (shift to the left in the figure). Figure 4 illustrates that in obstructive lung disease, patients are breathing on their maximal expiratory flow-volume curves even during tidal breathing. Flow-limiting segments exist in the same airways as normal subjects during forced expiration, but the segments are flow-limited during every tidal breath. Figure 5 illustrates this phenomenon with actual flow-volume loops from normal subjects and patients with severe obstructive lung disease.[9] The obstructed patients have preserved inspiratory flows and markedly reduced expiratory flows, with superimposition of their maximum flow-volume relationships on their tidal loops.

Figure 6 shows particle deposition in a characteristic patient with advanced emphysema. Like the normal subject who placed himself on the flow-volume curve by performing a forced expiration, a patient with obstruction has a similar deposition pattern, but this phenomenon occurs during tidal breathing. Particles that pass through the oropharynx during inspiration enter the central airways and traverse them without difficulty, because lobar and segmental bronchi are generally widely patent during inspiration in emphysema patients. Then the particles enter alveoli, with a few depositing by sedimentation, and, like cigarette smoke, the bulk of the aerosol is exhaled. During exhalation, however, the central airways collapse, turbu-

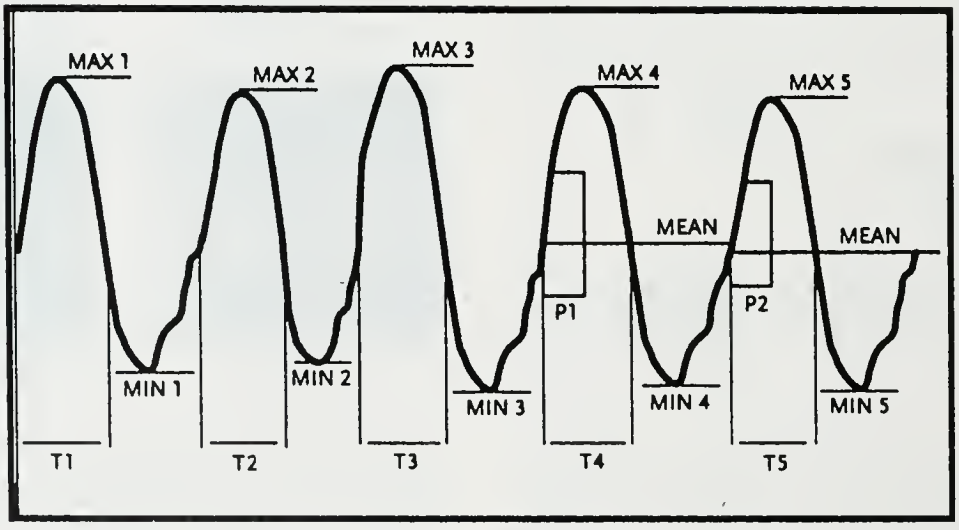


Fig. 11. Tidal breathing pattern measured by Halolite device. After 3 breaths, aerosol is injected as a bolus only during inspiration ($P_1 + P_2$, adaptive aerosol delivery). Total aerosol delivered to the patient (inhaled mass) is defined by the sum of the boluses. Pulse time = 50% of the sum of $T_1 + T_2 + T_3$. Dose = the sum of $P_1 + P_2 \ldots P_3$. (Courtesy of Profile Therapeutics, Boston, Massachusetts.)

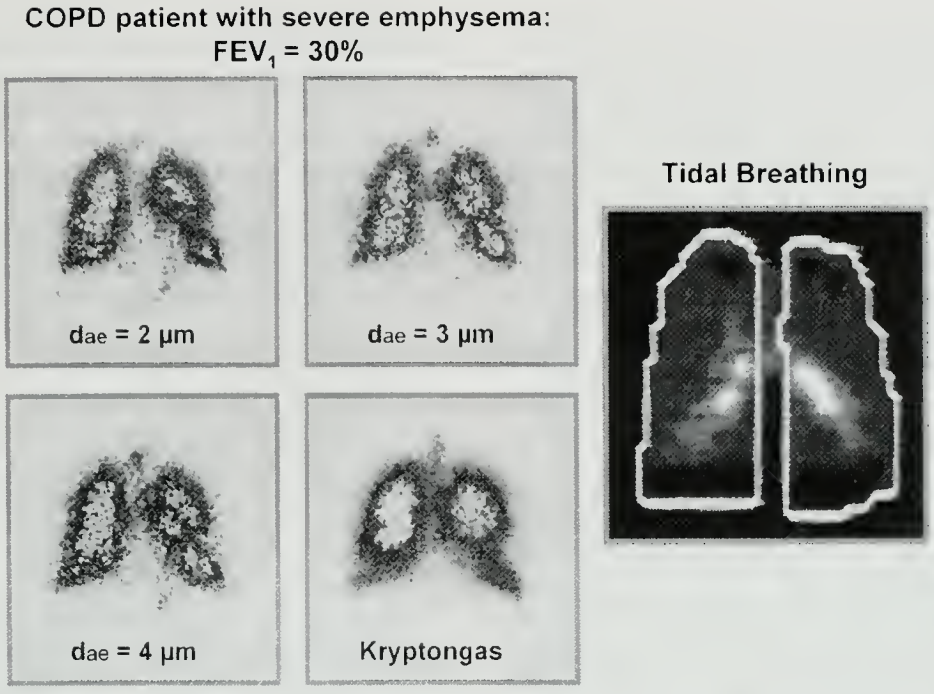


Fig. 12. Deposition images after aerosol inhalations from the AKITA device, with a patient with severe obstructive lung disease (left panels). Deposition appears to be peripheral for all particle sizes tested. The images mirror a ventilation image (krypton gas). The right panel is a deposition image obtained from a similar patient who inhaled the aerosol with tidal breathing. Differences in deposition pattern between the AKITA and tidal breathing reflect the different mechanisms of deposition: AKITA involves inspiratory settling, whereas tidal breathing involves expiratory deposition at flow-limiting segments. (Courtesy of InAMed, München-Gauting, Germany).

lence increases at the collapsed segments, and particles deposit at flow-limiting segments.[11]

### Variability in Particle Deposition

The paragraphs above illustrate phenomena that affect the regional deposition of particles within the oropharynx and lungs. Classically, clinical aerosols are delivered during tidal breathing. Figure 7 shows the variation in deposition in a group of normal subjects. When plotted against age, deposition shows a poor correlation. A somewhat better correlation is seen between deposition and airways resistance, a measure of airway geometry.[12] Table 1 shows the relationship of sex to deposition and airways resistance. Though the differences are small, deposition in female subjects is significantly higher, probably due to overall differences in airway geometry, with female cross-sectional lung dimensions being smaller than that in males, as indicated by the higher airways resistance.[12]

The major factor influencing deposition in normal subjects appears to be breathing pattern. As shown in Figure 8, the fraction of particles that deposit in the lung can be closely related to a parameter of ventilation that is similar to the period of breathing.[13] This would suggest that during tidal breathing deposition is controlled by sedimentation in small airways, influenced by local geometry (eg, the sex differences) and to a strong degree by the residence time (period of breathing). Table 2 compares data from normal subjects and patients with severe obstructive lung disease. As shown in Table 2 and as discussed above, in flow-limited individuals particles tend to deposit in central airways (higher central/peripheral ratio). In addition, the number of particles deposited per breath (deposition fraction) is also significantly higher in the flow-limited patients, all other factors being equal.[11]

In summary, total deposition in the lung during tidal breathing is a weak function of age and sex but a strong function of the period of breathing and the presence of flow limitation. Thus, in a given patient it is difficult to predict deposition and therefore the dose of drug. This is illustrated in the right panel of Figure 9, which is a deposition image from an asthmatic patient who inhaled from a conventional nebulizer (PARI LC Star). On average that device deposits 26.5 ± 5.72% of the nebulizer charge in the lung.[14] The variability of deposition, as shown by the standard deviation, is significant, averaging 20% between subjects. If the physiologic variables described above are the major factors involved in that variability, then a breathing pattern designed to minimize the airway geometry differences, control the period of breathing, and prevent expiratory events from increasing deposition to the central airways may control that variability. To study that possi-

bility, both the AERx and PARI LC Star devices were used with a group of patients (see Fig. 9). The AERx device is an aerosol generator that delivers particles only during inspiration, in a single, controlled breath. In terms of our physiologic review, it standardizes the period of breathing and minimizes exhaled particles. Deposition with the AERx (see Fig. 9) indicates a much higher mean deposition (80.0%), with a standard deviation of only 1.56%, which is only 2%, or one tenth that of the PARI LC Star. Though there are other differenees to be discussed between these devices, the variation in deposition is the key issue here, and that variation is reduced by an order of magnitude simply by controlling the breathing pattern.

## Smart Nebulizers

The emphasis in this review has been to summarize the relationship between aerosol deposition and basic variables of respiratory physiology. The major factors influencing deposition of aerosols are the breathing pattern and differences in airways physiology between inspiration and expiration. "Smart" nebulizers are designed to manipulate the breathing pattern to eontrol deposition, the efficiency of drug delivery, and the dose to the lung.

### Breath Actuation

The simplest of the "smart' devices is the AeroEclipse nebulizer (Monaghan Medical, Syraeuse, New York), which uses mechanical pressure-sensing components to sense a tidal breath and delivers aerosol only during inspiration, provided that the tidal volume is approximately 200 mL or greater. Figure 10 shows the AeroEclipse's output of aerosolized budesonide. For a tidal volume of 440 mL the device delivers approximately 35% of the nebulizer charge (inhaled mass), which is considerably higher than the delivery reported for conventional, continuously-operating nebulizers.[1] Figure 10 also shows the quantity of aerosol leaked from the device during expiration, which averaged $< 5\%$. When the device was used continuously (for smaller tidal volume), the inhaled mass was less, and, equally important, significantly more aerosol leaked into the ambient air. This finding demonstrates the importance of breath actuation in enhancing inhaled mass and reducing the quantity of leaked aerosol.

### Control of Dose During Tidal Breathing (Adaptive Aerosol Delivery)

As discussed above, delivering aerosolized drugs during tidal breathing is fraught with high variability. The HaloLite system (Profile Therapeutics, Boston, Massachusetts) was designed to standardize the dose. The HaloLite introduced the concept of "adaptive aerosol delivery," in which the device measures the patient's tidal breathing. I have observed considerable variability in breathing patterns between subjects when administering aerosols during tidal breathing. However, for a given subject the breathing pattern appears to be relatively well defined breath to breath. Adaptive aerosol delivery measures tidal breathing (Fig. 11), and after 3 breaths the device injects aerosol into the air stream only during inspiration. Though the breath-by-breath delivery of aerosol may vary between subjects, adaptive aerosol delivery sums the boluses of aerosol created on a breath-by-breath basis and therefore defines the inhaled mass for each individual. Adaptive aerosol delivery combines the attributes of breath actuation (better efficiency and less leaked aerosol) with greater control of the inhaled quantity of drug.

### "Slow and Deep" Aerosol Delivery Systems

In patients with obstructive lung disease the promotion of deposition in the peripheral lung poses a substantial challenge. In addition to the vagaries of tidal breathing, aerosol deposition is enhanced during expiration at sites of flow limitation. In addition, peripheral deposition is reduced in subjects who have emphysematous alveoli, because the settling of particles is minimized in the larger air spaces. Based on these physiologic considerations, peripheral aerosol deposition in these subjects would be favored with a system that provides a slow, prolonged inspiration (to promote deposition by settling) with a breath that is long enough to minimize the aerosol's availability to the airways during expiration. The AKITA system (InAMed, München-Gauting, Germany) is designed to do this. This system does not allow the patient to breathe tidally, but by providing a measured degree of inspiratory resistance, inhalation from a conventional nebulizer is controlled and the inhalation is slow and deep. Because the patient breathes against a fixed resistance for a long enough period, particles settle in the peripheral airways and only a limited quantity of aerosol is exhaled. In patients with severe emphysema this maneuver promotes peripheral deposition and minimizes expiratory deposition at flow-limiting segments. Figure 12 shows images from inhalations of 3 different particle sizes (2, 3, and 4 $\mu$m), each of which are consistent with a peripheral deposition pattern (similar to the distribution of an inhaled gas, lower right panel). The right panel of Figure 12 shows a typical image from tidal breathing in an emphysematous patient, with deposition at flow-limiting segments in eentral airways.

## Summary

Over the last 10–20 years the physiology of aerosol deposition in health and disease has been defined to the extent that manufacturers now have tools that allow the delivery of aerosolized drugs with an increasing degree of control. In the past the most common drugs delivered to

patients were extremely safe and dose control was of limited value. Beyond bronchodilators, however, dose control and device efficiency are increasingly important. For example, to treat pulmonary emphysema it is likely that $\alpha_1$-antitrypsin should be deposited in alveoli rather than central airways, but sophisticated devices are necessary to do this with any degree of control or efficiency. Equally important is the danger to caregivers from exposure to leaked and exhaled aerosols. Systems designed to maximize deposition before exhalation are beginning to address this problem.

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## Discussion

**Dennis:** I want to ask about occupational exposure to aerosolized drugs. In England we have the National Health Service, which is based on Victorian-era hospitals. About 15 years ago over half of the food poisoning cases in the United Kingdom weren't in schools or homes, but in hospitals, because they had exemption from Crown prosecution, so they had very poor standards of hygiene. Hospitals in the United Kingdom are still very slow to adopt health and safety improvements, so we have lots of occupational chemical exposure in hospitals that are not accepted in other industries. What is the story in North America? Why is it that we're allowed to expose health care workers? We know that we're exposing them, and we know that these chemicals can be classified as industrial agents, because they have health effects and sensitizations associated with them. Similar occupational exposure wouldn't be allowed in the pharmaceutical industry that manufactures the drug. Why do we allow this?

**Smaldone:** It's not really allowed. It's not addressed because it's not thought of. In *our* system when it was discovered in the case of our nurses, there was a dialogue with OSHA [the Occupational Safety and Health Administration], the responsible federal agency, which is usually called in by workers when they wonder if there's an exposure or if they should be concerned about something. NIOSH [the National Institute for Occupational Safety and Health] made measurements, and we took a lot of urine specimens for them during the pentamidine era. Then we addressed the issue in our hospital. If we don't address these issues up front, then sooner or later they're going to become public issues.

**Hess:** From what we can tell, OSHA and NIOSH have not even considered issues of caregiver exposure to antibiotics. We looked all over their Web site and we called people, and it seems that it's not even on their radar screen.

**Smaldone:** I think OSHA and NIOSH generally don't consider problems unless people demand that they do. They are responding agencies, not proactive agencies.

**Hess:** And the problem is that you're not going to know for years and years the effects on drug resistance from long-term, low-dose exposure to antibiotics.

**Smaldone:** Well, there are a lot of speculations, of course, about the effects of these drugs. It's best to address it up front. I can say from some work I did with Battelle years ago, that for the aerosolized chemotherapy agents there's a tremendous amount of proactive, protective attitude. But

that's at a knowledgeable organization that knows that it's going to have to deal with it.

**Hess:** And those are agents that pharmacists and others have been concerned about for years.

**Smaldone:** Correct.

**Fink:*** When exposure risks have come to our attention, with drugs such as pentamidine and ribavirin, there has been a response from the clinical community, with extensive efforts to implement guidelines to protect workers. Unfortunately those guidelines were more oriented to protecting workers than visitors, parents, or patients. We should promote better protection from second-hand aerosol exposure, with safeguards extending to protect anyone at risk of exposure.

**Smaldone:** I agree, and I think that a complementary approach is for the pharmaceutical companies to proactively process safety into their marketing plans.

**Geller:** In pediatrics we're stuck with a population that has to do tidal breathing technique. Some companies, such as Monaghan Medical with their AeroEclipse nebulizer, are working on making the breath-actuation part more sensitive, to make it useful with younger patients. Can you make any recommendations—short of abandoning aerosol therapy in infants—to optimize that?

**Smaldone:** We are just getting into that now. One of critical issues about delivering aerosols to infants is face mask physiology. There's a different physiology between spacer aerosol delivery and nebulizer aerosol delivery. Attention paid to face masks would provide for scenarios where, at least as a first approximation, we'd be able to standardize drug delivery for different age groups. There is technology available to control aerosol delivery in children. It's a wide-open area and we're just at the beginning of it.

**Fink:** My understanding is that the AKITA device integrates very slow, deep breaths with some "smart card" technology that measures certain of the user's pulmonary function variables and uses that information to achieve optimal delivery.

**Smaldone:** That's right. I don't have any experience with the AKITA, and the information I have on it was kindly supplied to me by Gerhardt Scheuch. I can't vouch for the data, but I think it probably does what they say it does. The smart card incorporates pulmonary function variables and their database of information on deposition. They believe they have a model that can predict deposition. The device measures the breathing pattern and coordinates aerosol delivery with the breathing pattern, based on their model. They've shown in scintigraphy studies and other studies that it's predictive.

**Gomez:** I want to discuss the relationship between lung deposition and the Stokes number. In general, meaning for all airways, deposition is strictly a Stokes number affair, and you started out on the right foot, but you seemed to depart from that conclusion, because you thought that there are other factors that come in; you mentioned particle behavior in pediatric patients. But perhaps everything can be interpreted in terms of the Stokes number, because the definition of the Stokes number has a particle time and a fluid time. The particle time is where the particle size comes in, as well as the particle density. For example, colleagues have worked on the density as well, to achieve distal lung deposition. Then you have the fluid time that varies. If you have turbulence, as you might in the upper respiratory tract, then fluctuations in velocity may affect the fluid time. So I'm wondering if, on that physics basis, everything can be interpreted in terms of the Stokes number.

**Smaldone:** I understand. I can't answer you with precision, but I think that if you can show me that, for example, the settling velocity equations are offshoots of the Stokes number, then I would agree with you. But I think that, from a superficial point of view, during tidal breathing, the period of breathing is the primary factor (superimposed on an airway geometry, an airway cross-section) that determines deposition. I don't know enough about fluid dynamics to say whether I can agree with you, but to me, settling velocity is not necessarily a Stokes-type relationship. It's a different type of phenomenon. But if you want to consider them equivalent, then I would agree with you.

**Gomez:** No. Settling is a different issue. Deposition, when it's controlled by the competition of inertial effects and viscous forces, depends on the Stokes number. In a quiescent environment settling kicks in, but before sedimentation can play an important role, particles must reach the distal region. To that end, control of their inertial behavior, and therefore their Stokes number, is critical.

**Smaldone:** Well, I think that in the periphery, during tidal breathing, settling is believed by most to be an important factor in deposition, although we don't really understand very well the convective nature of flow in the deep lung. And there can be convective forces that influence the transfer of particles, say, from tidal air to residual air and deposition. Fluid dynamics in the lung is a very interesting area, from a simplified point of view, which is why I went into medicine. There are clearly inertial effects

*James B Fink MSc RRT FAARC, Aerogen, Mountain View, California.

in the oropharynx and there are periodicity effects in the periphery that are controlled, at least in a gross sense, by the tidal breathing pattern. Bill Bennett's data are by far the best on that subject, and I think they illustrate that principle.[1]


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**McMahon:*** I want to ask about efficiency and breath-actuation. Breath-actuation will make nebulizers more efficient, so that a greater percentage of the drug will reach the lung. How is that being dealt with in the clinical setting as far as determining dose?

**Smaldone:** That's a good question. I'll give you my answer, and I am sure there are many other answers in this room. Device development and drug development often occur on different tracks. A lot of the devices that we've discussed at this conference have been developed independently of drugs. Manufacturers believe that efficiency is important, but it won't be shown to be important until it's linked to given drugs. If you use a more efficient device for a drug that's already on the market, then you have to deal with that efficiency. The bottom line is that physicians have to be educated about the devices they're dealing with. The basic issue regarding breath-actuation, for example, is that it's like any other tool. If you have a patient who won't sit there for 10 minutes, you can treat them for 5 minutes with a device that's twice as efficient, *if you know that you can do that.* But your question reflects the vagaries of device/drug development, and that's an issue that others here are going to have to address.

**Fiel:*** I want to reiterate that point. That is exactly the disconnect of the clinical arena from the development arena. The dose that is described is never the exact dose delivered, and even the area of deposition is frequently not known. I think the clinical side needs to work together with the development side so that we have a much clearer understanding of what is being delivered to the lung, so we can make a little more sense out of what we are doing. Another point that was brought up by Dean [Hess] is in relation to risks from aerosol contamination in the hospital, particularly with antibiotics in the intensive care unit, where drug resistance is a very important topic.

**Smaldone:** I think that right now antibiotics are not as commonly used as one would think. In the intensive care unit we use a lot of aerosolized antibiotics, using Stony Brook protocols. All those systems are filtered, and the exposure to caregivers is minimal, I believe. With regard to inhaled tobramycin, for example, in the hospital it's not clear what the exposure is to caregivers in, say, a single room in a hospital. Most of our cystic fibrosis patients get a private room and all their aerosol treatments are enclosed. I think it's important to consider caregiver exposure, but there's very little data on it and it needs to be studied. I would do it on a proactive basis.

**Stenzler:*** Selecting the particle size for different patients may be more important. For example, in COPD [chronic obstructive pulmonary disease] patients who have good air flow during inspiration, using a particle that's slightly larger, that isn't exhaled back into the central airways, may have a better deposition. What are your thoughts on that?

**Smaldone:** I think that if you combine the AKITA device technique with particle size, you can enhance deposition. But you have to use the AKITA technique. In other words, if you make particles larger, say, 4–5 $\mu$m, a COPD patient doing tidal volume breathing will still get central deposition and more oropharyngeal deposition. But with the AKITA technique, which involves a slow, deep breath, if you use bigger particles, the slow breath allows more of the large particles to get past the oropharynx, at least in adults; I don't know about in children. I believe they have data and my slides showed different particle sizes. And then you enhance the peripheral deposition. So a combination of those principles leads to a more effective delivery.

**Dolovich:** Gerry, could you add to the clinical scenarios for improving deposition and comment on receptor-site location and systemic delivery? Do we know where these drugs are being absorbed in the lung? Is the absorption from proximal or distal airways? Should drug delivery approaches be different for drugs targeted at the lungs, such as asthma drugs, than for drugs that use the lung as a delivery system?

**Smaldone:** That's a very good question. From a practical point of view, there's no such thing as an ideal drug delivery system for all uses. For example, the interleukin-4 receptor study[1] compared the PARI LC Star nebulizer and the AERx. The PARI had more central deposition. Is that *bad*? For asthma it's probably better. I don't have all the data from their clinical trials, but I think a lot of their trials were done with the PARI, and their preliminary data indicated that the drug was effective. There's no evidence that the drug would necessar-

*Carolyn McMahon, Allegiance Healthcare, Riverside, California.

*Stanley B Fiel MD, MCP Hahnemann University, Philadelphia, Pennsylvania (discussant for Monaghan Trudell, Syracuse, New York).
*Alex Stenzler, RPFT, VIASYS Healthcare, Yorba Linda, California.

ily be more effective if deposited peripherally. On the other hand, the bioavailability of insulin is better with peripheral deposition.

Regarding the mechanisms of drug transport, I'm not an expert, and I don't even know if it's fully known, but receptor site and clinical condition are specific to the clinical condition. As a physician you choose multiple drugs to treat different diseases, and sometimes the same diseases require different drugs in different patients. The same applies to aerosol delivery, in that you have to know something about this in order to design a treatment regimen for a patient. Our focus has to be on determining how physicians should treat their patients.


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**Stenzler:** This year and last year at the American Thoracic Society conference, the group from Brompton Hospital [London] presented data on monodisperse aerosols of 1.5, 3, and 6 $\mu$m. Interestingly enough, their scintigraphy scans showed that the small particles had the best lung distribution *but* the central lung deposition with the 6-$\mu$m particles had the best clinical response.[1]


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**Smaldone:** Right. That has been looked at by several other groups as well, over the last 10 years. For drugs such as bronchodilators the data suggest that central deposition is a plus. So, again, for the device manufacturers, you can't generalize in terms of one device for every situation.

# Standardization Issues: In Vitro Assessment of Nebulizer Performance

John H Dennis PhD MSc

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**The delivery of nebulized drugs is poorly controlled and the choice of the most appropriate delivery device is poorly understood, particularly because of off-license prescriptions and a lack of evidence-based medicine. Standardized in vitro methods for measuring nebulizer performance have been adopted in Europe, by the 2001 publication of a European Standard, prEN13544–1. These standardized methods were subsequently incorporated within the European Respiratory Society nebulizer guidelines, which will provide clinicians with useful information to improve nebulizer therapies. Standards for measuring nebulizer performance should be considered in North America and elsewhere. Careful consideration should be given to either adopting the methods embodied in the European Standard or developing the basis for developing that standard further through the International Standards Organization. Either way, confusion among clinicians would be reduced and nebulizer safety and aerosol delivery efficiency increased by standardizing in vitro methods of nebulizer performance assessment.** *Key words: nebulizer, nebulization, aerosol, standard, standardization, testing, Europe, International Standards Organization, ISO, Comité Européen de Normalisation, CEN, in vitro assessment.* [Respir Care 2002;47(12):1445–1455]

## Introduction

Although delivering nebulized drugs to the lungs has been used for centuries in medical research, and nebulizers and nebulizer drugs have been commercially available throughout the past century,[1] the delivery of nebulized drugs is still poorly controlled and poorly understood by the clinical community.

Prescription drugs delivered orally, intravenously, and via aerosol inhalation from metered-dose inhalers and dry powder inhalers undergo clinical trials to prove the drug's safety and efficacy. This is not the case with the many drugs used for nebulization, which are prescribed off-license and bypass regulatory requirements. Nebulizers are regarded as cheap and convenient plastic devices that readily generate an aerosol (Fig. 1) that will contain whatever drug solutions or suspensions are placed in them for delivery to the respiratory tract. Rarely is the nebulizer delivery device specified on the prescription. Rather, only

John H Dennis PhD MSc is affiliated with the Department of Environmental Science, University of Bradford, Bradford, West Yorkshire, United Kingdom.

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Correspondence: John H Dennis PhD MSc, Department of Environmental Science, University of Bradford, Bradford, West Yorkshire, United Kingdom, BD7 1DP. E-mail: j.h.dennis@bradford.ac.uk.

Fig. 1. A typical jet nebulizer, showing release of aerosol.

the drug solution volume and concentration are specified. This leaves open the choice of nebulizer by which to deliver the off-license drug aerosol. The decision of what device to use is often left up to the local doctor or nurse, and sometimes even a hospital clerk, to choose whatever device is either conveniently to hand or has become the hospital's standard nebulizer for that period. The nebulizer is often chosen with little or no objective justification other than the manufacturer's performance claims or, more often, simply the lower cost of a particular nebulizer. The reader should recognize that there is a wide range of performance among nebulizers. If, say, 2 mL of a given drug solution was placed into all available nebulizers, the dose delivered could vary greatly.[2] The lack of regulation and understanding in matching the prescribed drug with the nebulizer implies that the quality, consistency, and control of the delivered dose are poor.

There are 2 main types of nebulizer, jet (or pneumatic) and ultrasonic, which have different operating characteristics (recently reviewed by Hess[3]) and can be described in terms of their overall performance as either constant-output, breath-enhanced, or dosimetric.[2] Each nebulizer brand has specific characteristics that determine its aerosol output, including total rate of aerosol output, rate of aerosol delivered to the patient, dead volume (solution remaining in the nebulizer after nebulization has ceased), and particle size characteristics. Some nebulizers are most efficient at delivering small droplets to the peripheral lung, some nebulizers are better suited to deliver larger particles in the upper airways, and, in my opinion, some nebulizers are not suited to drug aerosol delivery at all. But how is the clinician to know which nebulizer to use for which patient? What criteria can the clinician use to make an informed decision?

Many methods have been described to measure the "performance" of particular nebulizer designs.[4,5] For instance, measurement of aerosol output using weight loss has been undertaken for decades and is still commonly used. However, weight loss measures both aerosol output and evaporated solvent, and evaporated solvent typically accounts for half of the weight loss over a nebulization period. In some particularly inefficient nebulizers, evaporation can account for more than 75% of the weight loss.[6] Alternatively, total aerosol output can be estimated by measuring the amount of drug solution left in the nebulizer cup. This method can provide a measure of the total drug aerosol emitted and is not confounded by evaporative losses, but it does not reflect the aerosol delivered to the patient, as most nebulizers commonly allow inhalation of only 40–70% of the emitted dose. There is a similar problem with methods that collect all emitted aerosol on a filter, followed by subsequent analysis of the filtered residue. Though all these methods produce data, the results cannot reflect the in vivo situation. This, in my opinion, makes them weak methods on which to base a nebulizer standard, as the results are divorced from the clinical setting.

Measuring aerosol particle size is equally confusing. Cascade impactors, which are commonly used to measure aerosol particle size from metered-dose inhalers and dry powder inhalers, can drastically distort the aerosol size by causing full evaporation of the nebulized aerosol. Laser diffraction (scattered light) size measurement of aerosol droplets cannot take into account droplet evaporation, which is inherent in all constant-output aerosol designs. For both aerosol output and aerosol droplet size many different results are possible from the same nebulizer, depending on the measurement method used.

The relative merits of the various methods to assess in vitro nebulizer performance have been debated in the literature for decades, often by individuals or small groups with greater or lesser amounts of training in aerosol and clinical sciences. From all the different views one common message emerges, namely that the method used should reflect the amount and droplet size of aerosol received by the patient.[7] In other words, the in vitro test should reflect the in vivo dose delivered. However, though that is a commonly held objective, over the past 50 years researchers have not naturally regressed to a commonly accepted nebulizer test method. And because nebulized drugs have escaped regulatory control, no national or international body had been commissioned to examine the science and produce standard methods. Or at least that was the situation

until the early 1990s, when the United Kingdom's standards body made the first attempt at standardizing test methods, by publishing a British Standard.[8,9] Though the British Standard methods had limitations (Table 1) the existence of the published standard became a focal point for debate and progress. In the late 1990s the issue of standardizing in vitro methods to assess nebulizer performance was tackled more comprehensively by the European Standards Organization (Comité Européen de Normalisation or CEN), culminating in the research and development of new nebulizer in vitro test methods published as a European Standard.[10]

The present review summarizes standardization issues inherent in the in vitro measurement of nebulizer performance, describes the scientific and clinical principles underlying the European Standard, introduces the principles underlying the clinical nebulizer guidelines recently published by the European Respiratory Society, and describes how the European Respiratory Society adopted the standard testing methods of the European Standard.

## Standardization Issues

There may be a perception that "standardization" could be interpreted as making things the same: making them a standard size, shape, color, or, in the case of nebulizers, similar in terms of performance, as measured by aerosol output and aerosol droplet size. That is not the intended meaning of *standardization* in this review.

There are many types, designs, and brands of nebulizer, with a great range of aerosol output and droplet size. I regard this as a good thing, because different drug solutions and suspensions are targeted to different parts of the airways, in different doses. Therefore different nebulizer designs are needed for different patients and settings (pediatric versus adult, intensive care versus home care), with different delivered aerosol doses and different droplet sizes required for different patients and therapies. Thus a wide range of nebulizer designs and performances are needed, ideally with each nebulizer medication being matched to a particular window of nebulizer performance. However, difficulty arises when clinicians are faced with numerous devices and manufacturer claims of performance characteristics. How should a clinician make the choice of what nebulizer system is best suited to a particular patient or patient group for effective delivery of a particular medicine?

In choosing the ideal nebulizer to deliver a particular drug, the clinician should take into account the intended site of aerosol deposition (upper and/or lower respiratory tract), which largely determines the required aerosol droplet size, depending on the patient's age and disease state, desired dose, treatment time, and patient compliance with the treatment. In addition, cost constraints can limit the choice of nebulizer. At present a major difficulty is that information on nebulizer performance is not presented to the clinician in any meaningful way.

Information on nebulizer output and aerosol droplet size can be entirely absent or only loosely described in marketing jargon (eg, "best performing nebulizer," "clinically proven," "preferred by over 90% of users") without any scientific justification of the claims. Of course not all nebulizer manufacturers are so vague in describing the performance of their devices. Many manufacturers actively promote, or at least have available, technical literature on their devices. However, those performance data can be obtained with a wide variety of laboratory methods. However well-informed the clinician, performance data are very dependent on the method by which they were obtained—so

Table 1. Strengths and Weaknesses of British Standard 7711, Part 3, Specification for Gas-powered Nebulizers for the Delivery of Drugs

| *Strengths* | *Comment* |
|---|---|
| First formal national standard relating to jet nebulizers | Focused attention on assessment of nebulizer performance and provided a platform for debate and technical research and development. |
| Adopted a chemical tracer rather than weight loss to evaluate nebulizer performance | Standard practice relied on weight loss, which grossly overestimated true aerosol output because of concurrent evaporation to compressed and ambient air. |
| *Weaknesses* | |
| No use of breathing pattern in assessing inhaled aerosol | This is particularly important for assessing the performance of breath-enhanced and dosimetric nebulizer designs. |
| Does not extend to ultrasonic nebulizers | Modern designs of ultrasonic nebulizers (eg, Omron nebulizer) have solved many past technical limitations and are expected to become more common as their advantages are recognized in the health care market. |
| Relies on laser diffraction to estimate particle size | Laser sizing takes no account of solute concentrating effects, particularly in the smaller particles, and provides a volume/size distribution invariably larger than the solute size (dry particles) distribution, which is of far greater clinical relevance and interest. |
| Applies laser diffraction to size a "standing cloud" | Nebulizer aerosols rapidly evaporate in ambient air, such as the air entrained over constant-output nebulizers or through breath-enhanced nebulizers. |

much so that the data may be meaningless, as with aerosol output measured by weight loss or solute loss, with or without breathing simulation. Yet that is usually the only type of information the clinician is expected to use in deciding about off-license nebulization of a drug. It is difficult if not impossible for the average clinician, who is not an expert in nebulizer design and function, to make an informed decision on which device is best for which patient. For that reason the focus in this review is to persuade the reader that some amount of standardization of in vitro aerosol measurement methods is desirable. Such standardization would provide a commonly derived data set for all nebulizer designs, which would (1) be more easily interpreted than the type of data currently available, (2) help clinicians determine the most appropriate nebulizers for particular patients and patient groups, and (3) improve patient safety and aerosol delivery efficiency.

At the risk of laboring the point for the need for standardizing nebulizer performance testing, consider the following analogy with the automobile industry. Cars come in a range of shapes and sizes and are intended for different purposes. Most car buyers know what basic design they require, but choosing the exact brand and model can be difficult. Like nebulizers, the manufacturer's marketing information is invariably biased toward its own product. Though this may make interesting reading for the enthusiast, it should not be relied upon for an objective decision. We can rely on reviews by experts who offer their opinions on subtle differences between models, but those views are individual and invariably biased by previous prejudices and current affiliations. Consider the information available for estimating fuel economy. If this important performance criterion were left solely up to the manufactures to provide, they would no doubt as an industrial group regress to making the measurement starting from the top of a mountain with a tailwind in order to bias the fuel economy figure as far as possible. That does not happen because standardized test methods for fuel economy have been developed to gain more realistic and comparable data. We must rely on objective information supplied by standardized methods to make an objective and fully informed decision. For example, data on trunk (called "boot" in the United Kingdom) space, acceleration, servicing costs, and depreciation are independently obtained. The methods for obtaining these data are refined to be as realistic and repeatable as practicable. Data that prove unrealistic are of little use. Methods that cannot be repeated are of little value. What is true for the automotive industry and marketplace is largely true for the nebulizer industry and marketplace.

To date there has been little, if any, standardization in the nebulizer industry and marketplace. I believe the industry would welcome standardization, as would most clinicians and nebulizer users. Standardization of in vitro performance measures would improve patient safety and aerosol delivery efficiency, and, in the long term, standardization can help provide a more solid foundation for development of better nebulizer technologies, because manufacturers will know that the marketplace is better prepared to recognize and appreciate the real benefits of new technologies. At present if a manufacturer produced a better nebulizer, how would the clinician know? It would just be absorbed into the marketplace as yet another "best performance" nebulizer claim, with perhaps a few supporting papers written by individuals with personal bias and affiliation. It is for these reasons that some standardization is required.

### European Nebulizer Standard

The European Standard developed over a period of 6 years, involving all European national standards bodies (eg, United Kingdom's British Standards Institution, Netherlands Organization for Applied Scientific Research) working within CEN, the European umbrella organization. Most scientists and clinicians with a serious interest in nebulizer testing and clinical application were involved, either directly or indirectly. For the first time, a critical mass of clinical and scientific experts were brought together to focus on how best to standardize the measurement of nebulizer performance. Though the European Standard on nebulizers addresses a number of regulatory issues, most are beyond the scope of the present review. What is important here is that the European Standard facilitated the development of in vitro testing methodologies that were thoroughly discussed and evaluated prior to acceptance by the European clinical and scientific aerosol community. Aspects of the European Standard have been described elsewhere.[11] Some of the more important principles are introduced and summarized below.

### Nebulizer Versus Nebulizer System

The European Standard recognizes that different nebulizers will deliver different doses of drug to the same patient, even if all conditions such as breathing pattern and nebulizer fill volume are controlled. This is because some nebulizers are inherently more efficient than others. For example, consider the most common nebulizer design, the constant-output nebulizer, which probably accounts for more than 70% of the nebulizers in home and hospital use today. A constant-output nebulizer emits aerosol at a constant rate until the volume of drug solution in the nebulizer cup is so small that nebulization ceases. The rate of aerosol output is constant, regardless of whether the patient is inhaling, breath-holding, or exhaling. This implies that for at least half the duration of operation the nebulizer is emitting aerosol into the ambient air. Not only is this extremely

wasteful, it is an important source of air pollution. Breath-enhanced nebulizers, on the other hand, release more aerosol during patient inhalation than during breath-hold or exhalation and thus are inherently more efficient. Dosimetric nebulizers are the most efficient because (at least in theory) aerosol is released only during inhalation, so the entire emitted dose is delivered to the patient.

However, it is not only the nebulizer design that is important in determining the performance of the nebulizer; the characteristics of the nebulizer itself can be critically important. With a jet nebulizer the greater the flow of compressed air through the nebulizer, in general, the greater the aerosol output and, usually, the smaller the particle size. So the compressor is an integral part of the nebulizer system. Another important aspect of the nebulizer system is the design and use of the mouthpiece (eg, whether the mouthpiece is valved for exhalation), which can significantly influence the quantity and quality of aerosol delivered to the patient. Alternatively, the mouthpiece might be replaced by a face mask, which can greatly reduce the amount of drug effectively delivered to the patient.

The European Standard recognizes the importance of the *nebulizer system* rather than simply the nebulizer itself. For this reason the European Standard specifies that nebulizer manufacturers should test performance of the *nebulizer system* as they intend it to be used. So, for example, if a nebulizer manufacturer sells a nebulizer sometimes with a mouthpiece and sometimes with a face mask, both of those 2 nebulizer systems need to be tested for aerosol output and size. Similarly if the nebulizer is recommended for use with various compressed air flows, the manufacturer is required to test each nebulizer system with the range of recommended air flows—the minimum, maximum, and typical average flow. This requirement to test each permutation can impose a substantial range of testing variables, but each permutation relates to a specific clinical condition of use to which the manufacturer is targeting the nebulizer product. Adoption of a *nebulizer system* concept will dissuade manufacturers or researchers from publishing performance information without also making reference to the system in which it was tested.

The European Standard does not require testing all nebulizer designs for their ability to nebulize all drugs. Most commonly prescribed nebulizer drugs are in aqueous solutions that also contain excipients and usually some concentration of sodium chloride. Some formulations are suspensions, with small, nearly colloidal solid particles within an aqueous solution, usually with excipients and sodium chloride. Most formulations intended for nebulization (by design or prescribed off-license) behave much like a simple salt solution, though admittedly a few drug solutions and suspensions do not because they are either extremely viscous, froth, or foam during nebulization, or have some other physical characteristic that causes atypical behavior. However, those are the exception. The European Standard recognizes that testing all forms of drug solutions and suspensions with all of the nebulizer systems combinations would be unreasonably burdensome. The practice adopted within the European Standard was to use a single test solution for all nebulizer system permutations. The solution adopted was a low concentration of sodium fluoride, which was chosen because: it has similar properties to sodium chloride, which is commonly used in nebulizer drug formulations; it is relatively rare in most laboratory environments, so contamination from other sources is minimized; and electrochemical analysis of sodium fluoride concentration (using a method similar to pH measurement) is relatively simple, low-cost, and sufficiently analytically sensitive.

## Measuring Aerosol Output and Aerosol Droplet Size Using the Methods in the European Standard

In vitro assessment of nebulizer output has been poorly understood and characterized, and numerous methods have been described to estimate output. Recently, a European Standard was published and is believed to contain methods for reproducible and robust in vitro measurement of nebulizer aerosol output and droplet size.

### Aerosol Output

Figure 2 illustrates the European Standard methodology for measuring aerosol output. The nebulizer system is attached to a breathing simulation device. A low-resistance electrostatic filter (simulating the patient) is placed between the breathing simulation device and the nebulizer system. The intention is that aerosol collected on that filter represents aerosol delivered to the patient under clinical conditions. The standard breathing cycle is a simple sinus flow pattern of 15 cycles per minute and 500 mL per cycle. This pattern was adopted because it is relatively simple to simulate and reproduce. Other breathing patterns were considered (eg, square waves, various inspiratory/expiratory ratios), but none was thought more appropriate as a single measure than the simple sinus flow pattern. Though this pattern is specifically defined in the European Standard, the methods used can be adapted to virtually any other breathing pattern. Whatever the breathing pattern, the nebulizer is filled with a volume of test liquid that contains a trace amount (1%) of sodium fluoride. With the breath simulation device running and an electrostatic filter in place, any aerosol generated by the nebulizer system that is drawn into the breathing system (the analogy of being inhaled by a patient) is collected on the filter. The fluoride residue on the filter can then be quantified.

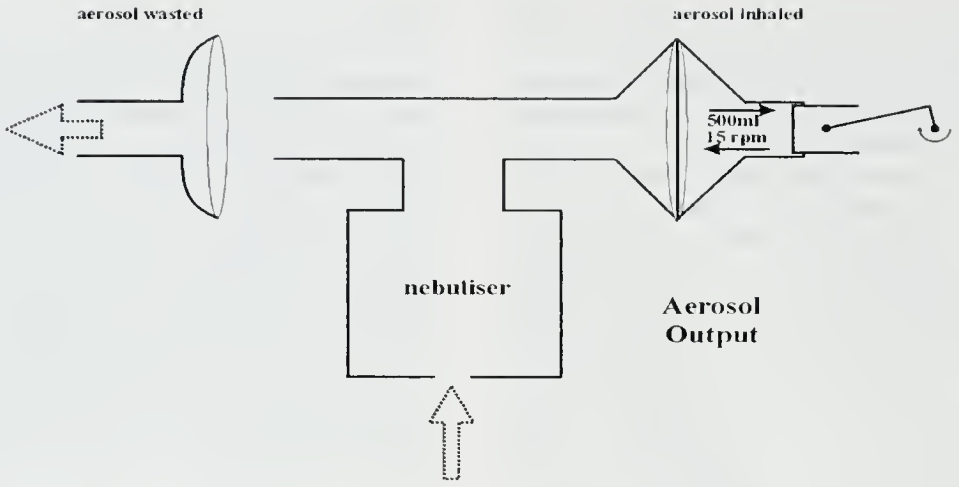


Fig. 2. Schematic of Comité Européen de Normalisation (CEN) methodology to measure nebulizer aerosol output. Aerosol output is subjected to sinus flow breathing simulation, and the aerosol is collected onto low-resistance electrostatic filters. The aerosol contains trace concentrations of sodium fluoride, which is quantified electrochemically. rpm = respirations per minute. (Adapted from Reference 12.)

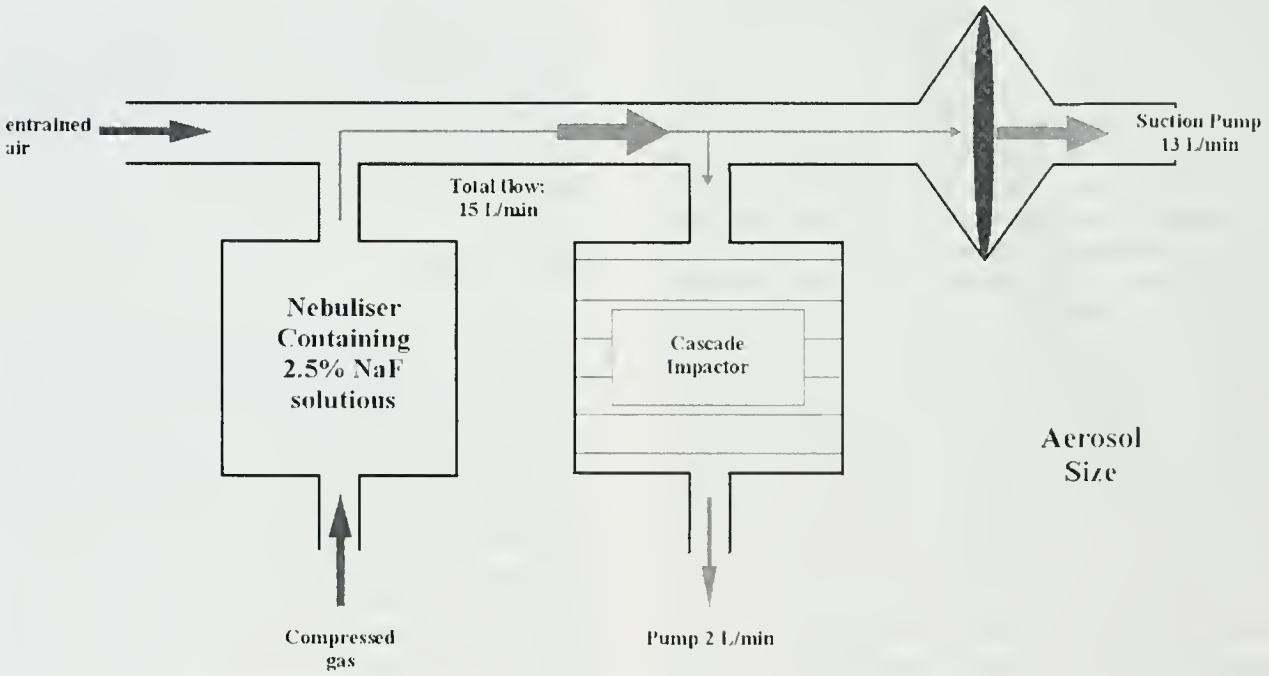


Fig. 3. Schematic of Comité Européen de Normalisation (CEN) methodology to measure nebulizer aerosol particle size. A constant inhalation of 15 L/min is drawn over (or through) the nebulizer. The nebulized solution contains sodium fluoride (NaF). The aerosol mixes with the entrained air. A 2 L/min flow is drawn off into a low-flow cascade impactor to sample the aerosol. The aerosol captured in the cascade impactor is analyzed for each size fraction, from which the normative and cumulative particle size distributions are derived. (Adapted from Reference 12.)

### Aerosol Particle Size

Figure 3 illustrates the European Standard methodology for measuring aerosol particle size. A low-flow cascade impactor is placed in line with the nebulizer system. The nebulized fluid contains a trace (2.5%) of sodium fluoride. Instead of using the dynamic air flow pattern of a breathing machine, a constant simulated inhalation flow of 15 L/min is applied, which is thought to represent a typical mid-inhalation flow rate. The cascade impactor samples a 2 L/min (2/15) fraction of the total flow. The aerosol droplets deposit according to size in the stages of the cascade impactor, and the amount of fluoride residue on each stage is quantified. Table 2 presents a sample set of cascade

Table 2. Worked Example of Data Obtained from a Graseby/Thermo Andersen Low-Flow Cascade Impactor

| A | B | C | D | E | F | G | H | I |
|---|---|---|---|---|---|---|---|---|
| | | Calculations to Process Size Distribution Data | | | | | | |
| Stage | Amount of Drug or Salt Assayed by HPLC on Each Stage (μg) | $\log_{10}(G_{stage1}) - \log_{10}(G_{stage2})$ [Δlog (Dp)] | B ÷ C [Conc/Δlog (Dp)] | $(G_{stage1} \times G_{stage2})^{\frac{1}{2}}$ [Geometric Mean Diameter (μm)] | $D_{stage} \div (D_{total}/100)$ [Conc/Δlog (Dp) normalized] | Cut-Point of Each Stage (from the impactor manual) [Dp (μm)] | Cumulative Summation of Material (derived from Column I)* [% < Dp] | Proportion of the Aerosol on Each Stage (derived from Column B by $B_{stage}/B_{total} \times 100\%$) [$V/V_{tot}$ (%)] |
| Top | 0.09 | — | — | — | — | 50 | 98.0 | 1.96 |
| Stage 1 | 0.09 | 0.85 | 0.11 | 32.63 | 1.32 | 21.3 | 96.1 | 1.97 |
| Stage 2 | 0.11 | 0.36 | 0.31 | 17.75 | 3.72 | 14.8 | 93.7 | 2.37 |
| Stage 3 | 0.41 | 1.00 | 1.00 | 12.04 | 11.94 | 9.8 | 85.1 | 8.61 |
| Stage 4 | 0.87 | 0.49 | 1.77 | 7.67 | 21.34 | 6 | 66.8 | 18.31 |
| Stage 5 | 1.49 | 0.54 | 2.76 | 4.58 | 33.25 | 3.5 | 35.5 | 31.33 |
| Stage 6 | 1.22 | 0.81 | 1.50 | 2.33 | 18.09 | 1.55 | 9.7 | 25.76 |
| Stage 7 | 0.35 | 0.51 | 0.69 | 1.20 | 8.26 | 0.93 | 2.3 | 7.38 |
| Stage 8 | 0.06 | 0.58 | 0.11 | 0.70 | 1.34 | 0.52 | 1.0 | 1.36 |
| Final | 0.05 | 0.73 | 0.06 | 0.36 | 0.75 | 0.25 | 0 | 0.96 |
| Total | 4.75 | — | 8.30 | — | 100 | — | — | 100 |

HPLC = high performance liquid chromatography
Dp = particle diameter
*Allows plotting the cumulative distribution curve against size
Mass median aerodynamic diameter = 4.4 μm.
(Adapted from the Graseby/Thermo Andersen Marple 290 cascade impactor operator manual.)

impactor data, from which are derived cumulative and normative size distributions such as those depicted in Figure 4.

## Clinical Relevance of the European Standard in Vitro Methods

It is not known how well the currently drafted CEN test conditions will predict clinical performance. This can only be established once an appropriate study has compared in vitro output and droplet size measurements against in vivo lung deposition with a variety of nebulizers. However, the European Standard in vitro methods were developed with the agreement of a number of leading nebulizer aerosol scientists and clinicians in Europe and were tailored to meet the needs of type testing within a European Standard and to be as clinically relevant as practicable. Preliminary work[13] relating draft in vitro methods in the European Standard to in vivo measures of aerosol deposition seem promising (Fig. 5), though more research is needed. If the European Standard in vitro methodology provides good estimates of in vivo deposition, then the in vitro methods could be used to guide clinicians in choosing the nebulizer system best suited for a specific patient group. If the in vitro/in vivo correlation is poor, then the in vitro methods can be examined and modified in subsequent standards to provide a more clinically representative measure of nebulizer output.

## European Respiratory Society Guidelines on the Use of Nebulizers

The in vitro methods in the European Standard are already being used to improve clinical practice. To appreciate the advantages of standardizing in vitro measurement of nebulizer performance, the following section introduces and describes basic principles underlying the clinical nebulizer guidelines recently introduced by the European Respiratory Society (ERS).

The ERS commissioned a task force in the mid-1990s to review the scientific and clinical principles of nebulizer therapy and to produce a set of guidelines (evidence-based whenever possible) to improve clinical nebulizer use throughout Europe. The task force held 3 interactive workshops, each with some 25 invited experts from throughout the nebulizer field, and the ERS Guidelines were published in 2001.[12]

The most important aim of the guidelines was to increase efficacy and patient safety by recommending systems by which nebulizers could be chosen and used. The guidelines were aimed at a wide variety of health care professionals practicing in very different health care systems throughout Europe. Though the immediate target au-

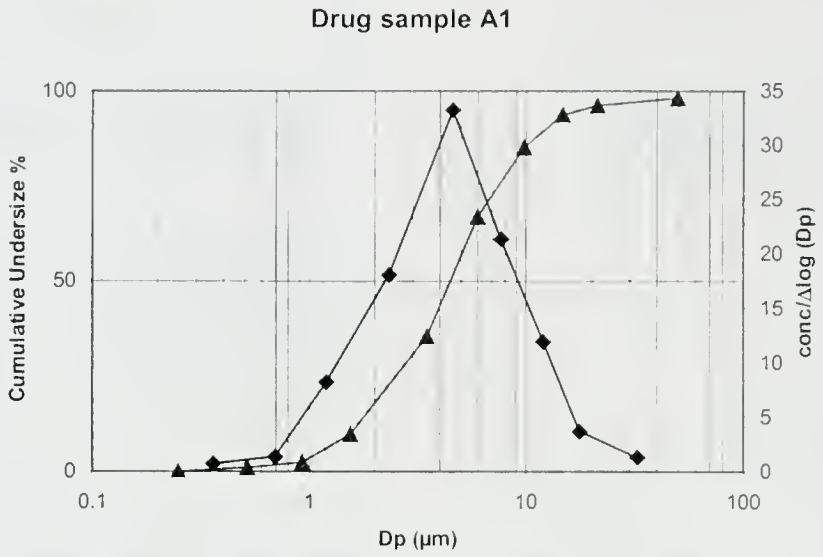


Fig. 4. Cumulative and normative distribution curves obtained from sample aerosol particle size data in Table 2. The mass median aerodynamic diameter is the particle size (in $\mu$m) obtained at the 50% cumulative undersize. Dp = particle diameter, conc = concentration. (Courtesy of Cora A Pieron PhD.)

dience was pulmonary physicians, the message was also aimed at all health care workers who are involved in delivering nebulizer treatments. The guidelines provided recommendations based on scientific and clinical evidence, and identified areas of ignorance where present practice is based on tradition or opinion rather than on scientific evidence. It was also hoped that by identifying gaps in present knowledge the guidelines would spur clinical scientists to undertake new trials to guide future practice. Full details of the background of the guidelines can be found in published supplements from the technical[14] and clinical[15] workshops and in the ERS Guidelines.[12]

For the present discussion the most important part of the ERS Guidelines is their technical reliance on the methods in the European Standard, which offer, for the first time, the opportunity to obtain a set of aerosol output data for each nebulizer sold in the European market—a comprehensive data set commonly derived from standardized in vitro methods. Hopefully each set of nebulizer performance data will closely reflect the in vivo performance. Further, the ERS clinical guidelines have adopted the distinction in the European Standard regarding the difference between a nebulizer and a nebulizer system, and the ERS clinical guidelines rely on data obtained from complete nebulizer systems.

The availability of clinically representative in vitro methods has led to the establishment and implementation of standard operating practices as a means of improving the efficacy of nebulizer therapy. These standard operating practices are embodied in the ERS clinical guidelines and are described below.

### Type Testing Using the European Standard

Nebulizer manufacturers in Europe are now required to test each of their nebulizer systems with a reference solution according to the European Standard. This will result in standardized information being supplied with every nebulizer. This information will include:

1. Description of the nebulizer system, including the flow rates and fill volumes tested
2. Rate of aerosol output and total aerosol output
3. Droplet size distribution curve, from which can be obtained the median droplet size, droplet geometric standard deviation, and percentage of aerosol mass within any given range (ie, $> 5$ $\mu$m, 2–5 $\mu$m, $< 2$ $\mu$m)

As mentioned above, the in vitro methods on which the European Standard is based are designed to reflect clinical conditions as closely as possible. The consistency of methods to obtain this in vitro information through the European Standard will essentially provide a type test of each nebulizer system, which will allow meaningful comparison of the performance of the various nebulizer systems and thus guide the optimal choice and use of those systems in clinical practice.

There are some important limitations in interpreting test data supplied by manufacturers complying with the European Standard. The first is that the data relate only to drug solutions that have properties similar to saline. Test data cannot be readily extrapolated to suspensions (eg, budesonide) or to solutions that have substantially greater viscosity than saline (eg, some antibiotics). The second is that the rates and amounts of aerosol delivery are obtained with

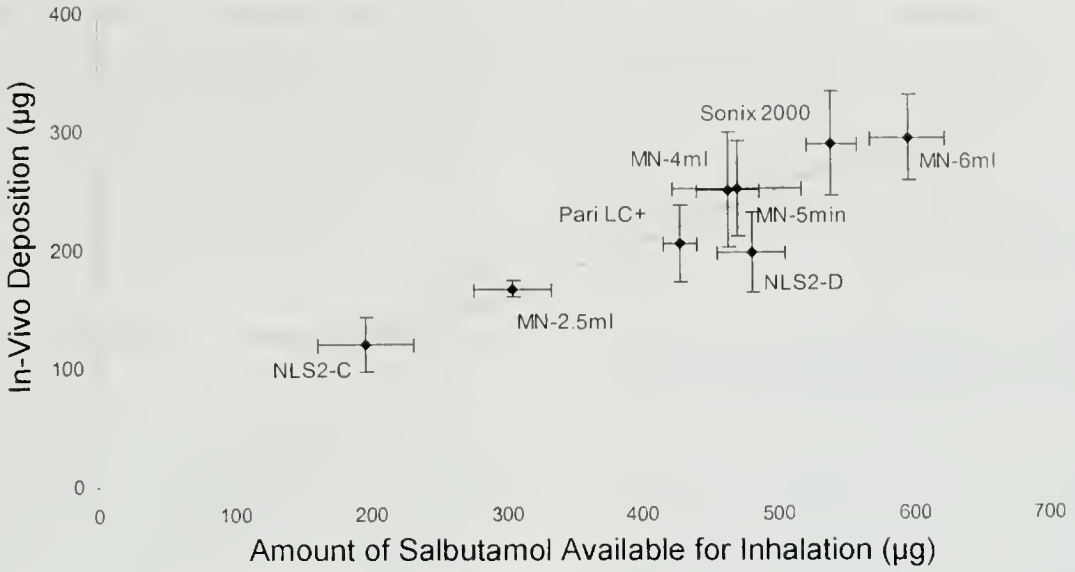


Fig. 5. In-vitro nebulizer performance measured with European Standard method (amount of salbutamol available for inhalation: X axis) versus in-vivo deposition (Y axis) (measured by urinary salbutamol and metabolized sulphate ester conjugate excreted 0–24 h following inhalation) with 8 nebulizer systems). $Y = 0.44X + 29.44$, $r = 0.94$, $n = 8$. Nebulizer systems: Microneb II chamber attached to a Medic AC-2000 compressor using: 2.5 mL fill volume (MN-2.5 mL), 4-mL fill volume (MN-4 mL), 6-mL fill volume (MN-6 mL), and 2.5 mL fill volume for 5 min (MN-5 min); PARI LC Plus with chamber using a 2.5 mL fill volume (PARI LC Plus) with a PARI Boy compressor; La Diffusion Technique chamber with 2.5 mL fill volume with an Atomiser Synchrone compressor (NLS2); Sonic 2000 ultrasonic nebulizer using a 2.5 mL fill volume (Sonix 2000). (Modified from Reference 13, with permission.)

a simulated adult healthy breathing pattern, and those data cannot be readily applied to pediatric applications or diseased adults. The test methods adopted within the European Standard are sufficiently flexible to accommodate additional test configurations.

### Characteristics of "Good" and "Bad" Nebulizer Systems

Nebulizer systems offer a wide range of performance, and how "good" or "bad" a system is depends on what it is intended to do. For example, if a system were required to deliver the maximum amount of useful aerosol (droplets between 0.5 and 5 $\mu$m) in the minimum amount of time, with a minimum of inconvenience, then the characteristics of a "good" system would include:

1. Fast nebulization rate, implying that the maximum amount of nebulized aerosol is potentially available to the patient over any given time
2. Minimum waste of drug aerosol, implying that maximum amount of aerosol is delivered to the patient and as little as possible is emitted to the environment
3. Low dead volume, implying that a high percentage of the fill volume will be delivered to the patient
4. Well-defined droplet size distribution

If, however, the same system were required to deliver only a modest volume of drug aerosol, then the system above becomes "bad" because such an efficient system will deliver an unnecessarily large aerosol dose, with possible increased local and systemic adverse effects.

The ERS Guidelines recognize that consideration must be given to matching nebulizer drug delivery to the performance of nebulizer systems. This requirement varies according to the needs of different patient groups and stages of disease. The 2 main factors to take into account are:

1. How much nebulized drug is ideally required for delivery to the patient? and
2. The droplet size required to maximize delivery to the intended site of action. Droplets $\ll 5$ $\mu$m tend to deposit peripherally, whereas droplets around 5 $\mu$m will mainly deposit in central airways.

The ERS Guidelines recognize that little clinical evidence exists to answer these questions, and it is therefore difficult to choose the ideal nebulizer system for a given application. So the Guidelines recommend that a scheme be developed to define the best available nebulizer systems for various therapies, to reduce variability in nebulized dose delivery, and thereby improve clinical practice.

### How to Select the Optimal System for a Given Patient Group or Specific Use

All health care systems throughout Europe currently have some system by which nebulizer drugs are prescribed for each clinical application. In addition, all prescribers and users of nebulizer drugs will commonly have experi-

ence using one or more nebulizer systems for each clinical application. Local practices will differ greatly, possibly even within an institution. Therefore the ERS Nebulizer Guidelines recommend that a standard operating practice be adopted for each nebulizer system in use. This would provide a baseline in determining the clinical effectiveness of each nebulizer system for each given application. That information could then be used to assess potential improvements to the nebulizer system.

## Implementation and Use of Standard Operating Practice As a Means to Improve the Efficacy of Nebulizer Therapy

### Standardize the Way Current Nebulizer Systems Are Used

If health practitioners can agree on a standard operating practice for the way in which nebulizer systems are used locally, then they can be sure that future clinical outcomes are patient-specific, rather than due to a change in drug output from the nebulizer. Nebulizer manufacturers can provide advice on the optimal operation of particular nebulizer systems.

### Assess Drug Output from the Current Nebulizer System

The scarcity of useful in vitro data describing nebulizer system performance has perhaps contributed to arbitrary choices of nebulizer systems. However, the standardization of nebulizer aerosol output and droplet size measurements made possible by the European Standard allows any given standard operating practice to be reassessed. For a specific clinical application the standard operating practice can be used in conjunction with data from the manufacturer to derive the dose delivered by that standard operating practice. That dose can be the total output, or it can be modified by the fraction of the aerosol in the optimal size range to determine a "useful" dose. If appropriate, one should also consider the potential systemic exposure from droplets not in the "useful" range, either by being too large and therefore depositing in the oropharynx, or by depositing in an inappropriate region of the lung and thus being directly absorbed into the systemic circulation and providing minimal local efficacy. Based on this approach, standard operating practices can be reassessed to see whether drug delivery can be further optimized by a change in one of the operating variables (eg, gas flow).

### Evaluate Alternative Nebulizer Systems

This information can be re-evaluated over time, as more efficient or cheaper nebulizers emerge. Consideration can then be given to altering prescription convention and/or adopting alternative nebulizer systems whose nominal delivered dose and droplet size (the standardized in vitro data from the manufacturer) are suited to a given clinical application. However, as with standardizing the way current nebulizer systems are used, substantial changes to standard operating practice should be monitored by appropriate follow-up of outcomes such as clinical benefits and adverse effects.

## Future Developments in Nebulized Drug Delivery

The task force drafting the ERS Guidelines anticipated that technical advances would drive improvements in nebulizer design. These performance advancements are being embodied in the next generation of nebulizers,[16] which are beginning to enter the market and will compete with more traditional jet and ultrasonic nebulizers. At the very least these new devices will offer substantial improvements in aerosol delivery efficiency. Though these systems can improve the quality of nebulizer therapy, there are risks if they are adopted with insufficient consideration of the consequences of efficiency improvements. However, if local practices adopt the above recommendations of instituting and reviewing standard operating practices, new and improved nebulizer therapies could be safely integrated with net benefits to patients. It is likely that newer, more efficient systems will deliver inhaled drugs more effectively and thus reduce the waste and the cost associated with inefficient systems. Clearly, standardization in measuring in vitro performance is required to safely make use of these new nebulizer technologies.

## Summary

Standardization of in vitro methods for measuring nebulizer performance would greatly reduce confusion and improve safety and efficacy of nebulizer therapy. The recently published European standard specifies in vitro methods for measuring and reporting nebulizer performance, and the data are expected to closely correlate with in vivo measurements of delivered dose and droplet size. The independent development of the ERS Guidelines took advantage of the European Standard and relied on the in vitro measurement methods therein to develop and recommend a common-sense strategy to improve clinical practice of nebulizer therapy throughout Europe.

Both the European Standard and ERS Guidelines are, by definition, intended to influence and improve the standard of nebulizer therapy in Europe. In practice, the in vitro methods described are universal, as are the recommendations to improve clinical practice. My final words to readers of Respiratory Care in North America and elsewhere outside Europe are that the standardization issues that have

been tackled in Europe are universal and apply equally in North America. If there is no good reason to adopt alternative in vitro methods for assessing nebulizer performance, then the methods in the European Standard can be adopted in North America or perhaps even by the International Standards Organization. This evolution would allow for any required changes and improvements to the European in vitro assessment methods that might become evident.

Some standardization in assessing in vitro nebulizer performance in North America is inevitable and required. However, the nebulizer manufacturing industry is very small in comparison to the pharmaceutical industry and can ill-afford a plethora of testing regimens. In my opinion there should be only one recognized standard for in vitro assessment of nebulizer aerosol. Developing a separate standard set of in vitro methods for North America defeats the purpose and would only serve to confuse the issues. I expect that the North American standards bodies will look closely at the methods adopted in Europe, and they should consider 2 options:

1. The in vitro methods accepted in Europe could simply be adopted in their entirety in North America, or

2. If fundamental problems are discovered with the European methods, or alternative methods are found to be more closely correlated with in vivo response, then a dialogue and cooperation among interested organizations in North America, Europe, and elsewhere could build a new set of methods in an international standard.

Either way, a single set of in vitro methods would result, which could be used in the absence of clinical trials to guide clinicians in choosing appropriate nebulizer systems.

The worst-case scenario would be that different in vitro testing methods (that yield different results for different nebulizer systems) be adopted in different countries. This would act to retard progress and increase confusion, and therefore must be avoided.

At present it is difficult if not impossible to meaningfully compare in vitro nebulizer performance data because of confusion about methodology and nebulizer operation. If a single in vitro measurement method such as the CEN standard were widely adopted, then nebulizer output data from different nebulizer systems could be meaningfully compared and evaluated.

ACKNOWLEDGEMENTS

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## Discussion

**O'Riordan:** I certainly agree with you that these European standards are much more sophisticated than anything that's gone before, but nevertheless I want to sound a note of caution, which is that when we look at lung modeling data for aerosol deposition, we're relying on the work of investigators who use monodisperse solid particles in healthy individuals. With nebulizers we're usually dealing with unstable, polydisperse, aqueous aerosols in people with diseased lungs. We therefore don't really have a great way of linking in vitro to in vivo data, so I think we should use the standards to work backward.

For example, let's say you do a study of cystic fibrosis and you prove that a particular dose of tobramycin is safe and effective. Then if that nebulizer becomes unavailable, you can use

those data to find a nebulizer that is as close as possible to the nebulizer that was used in clinical trials, assuming that you'll get comparable safety and efficacy. It's much more risky to use the standards as absolutes, in such a manner that someone may claim, "Well, I've just designed a nebulizer, and it's got this particle size and this output, and therefore it's *better* than the one that was used in the original clinical trial." That's a big assumption. I think we should play it safe and try to duplicate the nebulizer that had been used in clinical trials, because at least we know the safety and we know the efficacy. If somebody comes up with a nebulizer that's supposedly twice as good, they should have to do a clinical trial to support that claim.

**Dennis:** I think you're talking about a very specific application, and I think that would be a matter for a specific review body to look at. I've got no issue with it. What I'm getting at is the idea of leveling the playing field and getting one consistent and meaningful set of methods to describe *a* nebulizer's performance.

**Fiel:*** I think the concept of standards is absolutely necessary for where we're going, in trying to pull together the clinical outcome and the production of the various devices that are coming along. Still, I think that's a really good point that Tom O'Riordan made. And how it'll work out in the clinical arena remains to be seen. Up until now most of what clinicians have dealt with has been bronchodilators, where it really doesn't matter where and how you deliver, but it's going to be a whole different field soon and we're in for some problems if we do not standardize. John, do the European Standards have specific methods for the breath-actuated nebulizers?

**Dennis:** The breath-actuated nebulizers will just slip into the testing regimen for flow cycles, because they come on during inhalation and shut off during exhalation. So they *will* work within the testing method. For example, the HaloLite and the Aero-Eclipse both trigger during inhalation, though there may be an issue with whether they trigger soon enough at the lowest inspiratory flows.

**Dhand:** I was really interested in your engineering solution to make smarter physicians. To borrow a phrase from Alessandro [Gomez], I think we are heading for a "Coulombic explosion" with new nebulizer technology. I think a comparable issue is administration of antibiotics. There are specific indications for the use of an antibiotic, and then there are also specific indications for when you *don't* use them. I think for physicians it might be very helpful if nebulizer solutions came out with specific indications for which population they should be used with, how they should be used, and in which situations they should *not* be used.

**Dennis:** The ERS Guidelines look at the evidence for that and they make summary statements and recommendations.

**Smaldone:** I'm getting nervous. I have no problem with standards, but to me as an engineer, one standard is to look at a nomogram and the conditions for the measurement are there, and the data are there, and you do what you want with it. My problem with the so-called "standards" that have been discussed here are adjectives such as "meaningful," "appropriate," "better," "worse," and "recommended."

**Dennis:** "Consistent."

**Smaldone:** "Consistent" to me is simply the quality of the laboratory. If there's a nomogram with outputs on it, they'll have plus-minus sign on it, and there'll be a statement of—

**Dennis:** Oh, I meant consistent between laboratories—when different laboratories test the same nebulizer system and the results are similar, the results are consistent.

**Smaldone:** I'm simply saying that I'm opposed to all those other adjectives. I think a standard is a functional statement of a device: that's it. And that I don't want a regulatory agency telling me what's *meaningful* or not. I think that as a physician I ought to be able to make my own decision as to what's meaningful. Standards have been developed properly for MDIs [metered-dose inhalers] because of the attitude regarding cascade impaction and output measurements for MDIs, specifically that it's done primarily for quality control. The Food and Drug Administration sets relatively strict standards, and aerosols are measured, and that's about it. But all those adjectives are really a form of marketing, and I don't think they should be associated with a regulatory matter. You can still make the measurements, but they're whatever they are for whatever reason, but not a "standard." To use adjectives such as "better," "worse," and "meaningful" and make recommendations based on a standard that may have no relevance is, I think, very dangerous.

**Dennis:** I want to say a couple of things to that. MDIs undergo clinical trials, so we've got good information on MDIs, so we can afford to ignore the in vitro results. The in vitro tests can be considered just type testing and tossed into a drawer, just to be considered a money sink. But, for the most part, nebulizers don't have clinical trials, so what information are you going to use? If you were just another busy clinician looking for a nebulizer and didn't know much about aerosols or nebulizers, what information would you use to choose a nebulizer? That's

* Stanley B Fiel MD, MCP Hahnemann University, Philadelphia, Pennsylvania (discussant for Monaghan Trudell, Syracuse, New York).

what *I'm* talking about, that's what the ERS Guidelines are targeted at, and that's what we'll use the European Standard methods to provide: consistent information on aerosol output and droplet size from each nebulizer system. Consistent information that allows us to at least compare like with like. That information is not available at the moment.

**Gomez:** I want to comment on standardization of droplet size measurement techniques. The ERS standards are certainly acceptable and should be enforced. You mentioned that the laser diffraction technique may not be the best. If you are referring to the Malvern instrument, in the "droplet community" the Malvern has been almost completely supplanted by phase Doppler anemometry, which simultaneously measures droplet size, droplet velocity, and gas velocity, so that we have all the variables that are relevant for inertial based deposition.

**Dennis:** That works for you, but we're dealing with an aerosol that's evaporating at the same time that we're interested in the solute concentration, which you can't measure with phased Doppler, because the solute is concentrated. You don't know how much a droplet has been concentrated by, so a 2-$\mu$m particle might contain as much drug as a 5-$\mu$m particle. There's a dynamic operating that you can only measure by cascade impactor, at least with the existing technology.

**Gomez:** Wait a minute. You can model based on evaporation loss, because the volatile solvent evaporates and the solute stays behind.

**Dennis:** There's a couple of guys who have put their whole careers into such modeling, and they are still struggling away to try to get their modeling results to match the experimental data. It's not my field, and I admit it's possible, but it's certainly complex and is still indirect.

**Fink:*** It occurs to me that product information for many commercial aerosol products use similar units of measure for very different methodologies, on occasion using totally inappropriate devices to measure particle size. For instance, systems designed to make gravimetric measures of dry powder are totally inappropriate for jet nebulizers aerosolizing normal saline. This is how you see claims of 0.9-$\mu$m particles from a nebulizer that produces particles that measure $> 5$ $\mu$m by direct assay with a standard cascade impactor. Unfortunately, the manufacturer's data are often the only data the consumer has to make the device selection decision. In our laboratory we have tested a variety of nebulizers used for home care, finding inhaled mass ranging from 6 to 55%, with no relevant data in the manufacturer's literature. Do clinicians need to know that their choice of nebulizer may result in a 10-fold difference in drug delivery for their patient? Some standard for comparative measurement and reporting may have merit.

**Witek:*** My comment covers all of the presentations this morning, but particularly Gerry's [Smaldone] thoughts about marketing, advertising, and adjectives. I think it's important to understand that words such as "superior," "equivalent," and "noninferior" have very specific meanings in the design of a study, with respect to a priori statements on how your statistical analysis is designed. The important thing is that we in the industry have to define those and state such aspects a priori, and when we meet those requirements, then we're allowed to use those adjectives. Consider some of the data we saw today, for example: what's an "equivalent" response in $FEV_1$ [forced expiratory volume in the first second]? In a simplified example, some may say you take your peak response relative to placebo, and if it falls within a third of that response, you may have "equivalent" response in $FEV_1$. So, in some sense, with regard to the clinical data, there is some degree of a level playing field in that you need substantial evidence on what you say a priori you're testing.

**Dolovich:** I want to follow up on Jim Fink's comment. The Canadian standard that we developed for spacers has built into it testing the spacer with 3 drugs, so that we can compare different devices with the same type of drug. The manufacturer has a choice within the drug category, but it is anticipated that some drugs tested will be common to many of the manufacturers. Is that type of requirement also part of the CEN standard?

**Dennis:** Testing with drugs is not part of the CEN standard. The CEN standard is for generic testing of nebulizer performance, using a simple salt solution. However, the CEN standard allows for testing of drugs, since the analysis part can be adapted to high-performance liquid chromatography or other methods.

**McMahon:*** From a manufacturer's perspective, I believe you will find support for implementing standardized test methods for nebulizers. I do not believe the data will answer all of a clinician's questions; they will not dictate which nebulizer to use in various clinical applications. They should, however, help with credibility in advertising and literature, specifically in regard to measurements of MMAD [mass median aerodynamic diameter] and the percentage of respirable droplets. Several variables, including temperature, humidity, and flow rates, influence MMAD and the percentage of

* James B Fink MSc RRT FAARC, Aerogen, Mountain View, California.
* Theodore J Witek Jr DrPH RRT FAARC, Boehringer Ingelheim, Ingelheim am Rhein, Germany.
* Carolyn McMahon, Allegiance Healthcare, Riverside, California.

respirable droplets, so data from testing in various laboratories may not match what is in the advertising and literature for the device. So it would seem beneficial to have a standard test for nebulizers to determine MMAD and percentage of respirable droplets. It would clarify the test conditions used to obtain the data in advertising and literature.

**Dennis:** Yes, I agree. A nebulizer that came into Britain from Italy supposedly had 100% respirable aerosol. It was fantastic, and it was all the rage. But they had measured the particle size using saline and the TSI particle sizer, so it was just dry powder generated by the method of measurement! Not clinically representative at all. And they got away with it! They sold and they made money. People talked about the adjectives. I've deliberately tried *not* to use adjectives, and generally tried to say that "good" and "bad" can mean the same thing, depending on the application. It's the application the clinician should focus on.

**Berg:*** But there's nothing in the standards that indicate that you should test any drugs.

**Dennis:** I agree in part. The main purpose of the CEN standard is to end up with a CE mark [Conformite Europeene mark, on a product, that indicates the manufacturer has conformed with European product safety regulations] and say it passes the criteria of safety, plastic robustness (for instance, parts aren't going to fall off into a patient's lung), electrical safety, and all the other things that any safety organization would normally look at. But the CEN standard also needed some measure of aerosol output and size. Besides those other things, the CEN standard was always focused on providing a measure of output, some measure of nebulizer "performance." We tried to make sure the methods were as *useful* as we could make them.

The manufacturers will have to test for the CEN standard in any case, whatever the method. You *can* throw drugs into the equation and collect drug information, if you want to extend the CEN testing to that as well as the generic simple salt solution. So, in summary, though the primary purpose of the whole CEN standards organization and funding is for type testing (which is really behind-the-scenes manufacturing stuff), it has been adapted so its results become clinically useful, which they otherwise would not have been.

**Berg:** But there's nothing in the standards that say that you *should* test any drugs.

**Dennis:** It's actually *in* the standard that you *can*, but that drug information would not be reflected in the output generated for the CE marking, which is restricted to the output obtained with the simple salt solution. But you could extend the CEN study tests to using drugs in the nebulizer cup. The drug could change the output if, for example, it were more viscous. Alternatively, the drug could be a suspension. It is written in the CEN standard that you can apply it generally, but the CEN standard also warns against extrapolating the salt solution results to what will happen with the nebulizer drugs. If you want to know how a certain drug will perform in a certain nebulizer, test the drug or ask the manufacturer for the data. That's what the standard and guidelines recommend.

However, what the CEN standard does require as a minimum is that the manufacturer provide detailed output data (for simple salt solution, not drugs) on the nebulizer packaging, in order to get a CE mark. This provides the level playing field. This provides simple aerosol output and droplet size information for every nebulizer system with a CE mark, which is clinically useful comparative information. I believe this is an advancement on the current situation, which is very confused.

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* Elna Berg, AstraZeneca, Lund, Sweden.

# The Future of Nebulization

Peter W Barry MD

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Summary

**Currently available nebulizers are inefficient, bulky, noisy, and take longer to use than other inhalation devices. Use of nebulizers is increasingly confined to patients who cannot use other devices or who require therapies not available in another form. In the future, nebulizers will be smaller and more efficient. "Smart" nebulizers that can monitor patient use and provide feedback to the patient and the caregiver will be developed. Critical study will be needed to determine whether these innovations improve patient compliance with therapy. Nebulizers will also be refined for delivering complex molecules for both pulmonary and systemic disease. One example is in the use of gene therapy, in which issues such as the best gene vector are unresolved. Nebulizing these complex molecules without damaging them may be difficult, and nebulizers of the future will have to be more efficient to avoid wasting expensive drugs. For the delivery of widely used, less expensive medications, such as some bronchodilators, these innovations will not be cost-effective, so cheaper, less efficient nebulizers will continue to be used.** *Key words: nebulization, nebulizer, aerosol, vaporizer, critical care, surfactant, gene therapy, persistent pulmonary hypertension of the newborn, PPHN.* [Respir Care 2002;47(12):1459–1469]

## Introduction

Looking into the future is an attractive pastime for a number of reasons: you can champion causes that are dear to your heart; other people cannot contradict you, at least not in the present; and, as long as you predict far enough into the future, you are unlikely to be around to hear the opprobrium of your successors that the predictions were wrong. However, prediction is also a difficult pastime, with many potential outcomes and areas to be covered. In this review I will concentrate on a small number of clinical situations to illustrate some areas in which nebulizer therapy may be developed.

Our path to the future is influenced by our starting point in the past and by how we have traveled to get to our present. Inhalational therapy has a long history, with vapors and smokes being used in the treatment of respiratory disease and other ailments more than 4,000 years ago.[1-4] In the modern era, Sir Alexander Crichton described the use of the vapors of boiling tar in the treatment of tuberculosis, a practice continued in Berlin in the first half of the nineteenth century. In 1859 a portable device was marketed in France that generated an aerosol of liquid tar for medicinal use. Many types of nebulizer have since been developed, but the commonest type in use today remains similar in principle to the Collinson nebulizer,[5] a jet nebulizer constructed of ebonite with a plate baffle to filter out large drug particles. Until recently, improvements in nebulizer therapy have been made by modifications of that type of device.

Other reviews in this and the previous issue of RESPIRATORY CARE have documented the characteristics of the main nebulizer types and described various approaches to improve the efficiency of the jet nebulizer, as well as new approaches to nebulization that are being developed. This review will use examples from clinical practice to speculate on how nebulizers may be used in the future, to address 3 issues:

- Patient compliance with inhaled medication therapy
- Using complex or expensive drugs to treat lung disease
- Delivering complex molecules for gene therapy

## Compliance and Adherence

Patient compliance with therapy may be defined as patient behavior consistent with instructions from a doctor or other health care professional. This view of patients passively responding (or not responding) to commands from powerful physicians has been challenged. The terms "adherence," "therapeutic alliance," and "concordance" have been proposed[6,7] as a way of suggesting that a management plan consists of an agreement between a physician and the patient. Noncompliance may be seen as a failure of the physician and the patient to reach an agreement, as a failure of communication. Other factors that may also affect compliance include the drug regimen, drug formulation, and perhaps the drug delivery device.

Patient compliance with inhaled medication instructions is poor. In studies using electronic timers attached to metered-dose inhalers, and in which subjects knew that compliance was being monitored, on only half of the study days was the prescribed medication taken, whether this was self-administered by adults or children[8,9] or supervised by a parent.[10,11] Poorly compliant patients are at increased risk of exacerbations,[11] and it has been speculated that under-use of anti-inflammatory medications with relative over-use of bronchodilators increases the risks of fatal asthma.[12-14]

The most effective inhaler for any given patient is the one that the patient will use on a regular basis and in an effective manner. Nebulizer design factors that improve compliance are not known. Table 1 lists factors that *may* improve compliance, which are discussed below.

### Size

Although there is no evidence that compliance is improved by changing to a different inhaler device, small, unobtrusive devices are often marketed on the basis that

Table 1. Factors That Influence Compliance

- Size, portability, obtrusiveness
- Appearance: color, material, decoration
- Fashion
- Noise
- Power source (battery, car adaptor, wall outlet)
- Administration time
- End of life/treatment/dose-remaining indicator
- Interaction with patient/patient and physician feedback
- Multiple doses
- Effectiveness

Peter W Barry MD is affiliated with the Department of Child Health, University of Leicester, Leicester, United Kingdom.

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Peter W Barry MD has received or is receiving grants to support his research from major pharmaceutical companies and device manufacturers, including AstraZeneca, GlaxoSmithKline, and 3M Healthcare. He is currently involved in a commercial project to develop a "smart" spacer device.

Peter W Barry MD, Department of Child Health, University of Leicester, Clinical Sciences Building, Leicester Royal Infirmary, PO Box 65, Leicester LE2 7LX, United Kingdom. E-mail: pwb1@le.ac.uk.

they are more acceptable to the patient and will therefore be used more. There is little published evidence that these claims are justified.

### Appearance

There is no doubt from marketing studies of nonmedical appliances that the appearance and style of an object can affect its acceptability to a consumer and perceptions of a device's effectiveness. This is also linked to fashion (see below). Whilst there are many studies of the "8 out of 10 patients said they preferred the color of the new device compared to the one they are currently using" variety, there is little evidence that appearance by itself affects compliance or effectiveness of nebulizers. In pediatric practice, one company produces nebulizer attachments that give the nebulizer the appearance of a cartoon character. We have yet to see co-marketing of devices with famous characters from the entertainment or sports industries, and it is not known whether a medication can be made more palatable (to children in particular) by associating it with a particular character, although this appears to be widely accepted by parents in relation to other commodities.

### Fashion

There are large international differences in the use of different types of inhalable drug delivery device, which cannot be explained by differences in patient population or disease characteristics. As noted above, patients may be affected by the appearance of a device. Both patients and physicians are affected by peer pressure or fashion in their choice of other commodities, and it is clear that the prescription of different devices by physicians is to some extent driven by personal preferences that are affected by peer pressure, media exposure, and the prescriber's background.

### Noise

Jet nebulizers in particular can be noisy[15] and this may reduce acceptability, especially if obtrusiveness is perceived to be a problem affecting compliance.

### Power Source

Nebulizers that need wall-outlet power may be less easy for patients to use than those that run on batteries or alternative sources such as car batteries. Devices with self-contained power sources that do not run out or need recharging may be preferable, but to my knowledge there are no published data on the effect of power source on patient compliance.

### Administration Time

Despite research documenting the reduction in nebulizer output after a relatively short period of time,[16,17] nebulizers continue to be used "until dryness" or "until sputtering occurs." High-output nebulizers have been developed that deliver medication quickly and are said to improve patient acceptability. However, the high output may also lead to increased drug waste to the environment and, paradoxically, reduce drug delivery.[17]

### End of Treatment/Dose-Remaining Indicators

Associated with the issue of administration time, the facility available in some devices that indicates when drug administration is completed may also improve device acceptability.[18] This may take the form of a simple, timed on/off indicator, a detector of when the nebulizer chamber is empty, or a more sophisticated detector that measures the volume of aerosol leaving the device.[19]

### Interaction with Patient/Patient and Physician Feedback

There is increasing interest in drug delivery devices that can both monitor and prompt patient use and that can provide patient management data for the physician.

### Multiple Doses

Most nebulizers and some dry powder inhalers need to have the medication added to the device at each use, which necessitates carrying the device and the drug separately. This makes the device less portable and increases obtrusiveness, both of which may affect compliance. Patients also say that they prefer medications that can be given once daily,[20] but it is not known to what extent switching to a once-daily regimen actually improves compliance.

### Effectiveness

Not all noncompliance leads to poor outcome, particularly in mild disease, but does poor effectiveness of the prescribed medication lead to noncompliance? Perception of effectiveness is important. Medication that has an immediate effect on patient symptoms may have greater compliance than one given as a prophylactic therapy, in which case the benefits are not immediately apparent. There are no data comparing patient compliance with otherwise identical devices of different effectiveness.

## The Future

We know a little about the nature and extent of noncompliance, but almost nothing about the factors that improve compliance. For instance, patient contact with specialist asthma nurses is helpful,[21] but we do not know what aspect of this contact improves compliance.

Future nebulizer designs may address compliance by being easier for patients to use or by incorporating features that remind patients to take their medication. Table 2 lists some of the options that may be incorporated into future nebulizer designs. Whatever innovations are used, it is important that they are evaluated fully in properly conducted clinical trials. A complicating factor is cost. Some of these options may be expensive to incorporate into nebulizer designs, and this may not be economical for (1) the delivery of inexpensive drugs such as $\beta_2$ agonists, (2) drugs with a shallow dose/response curve and a large effect/adverse-effect ratio, where a larger nominal dose can be safely administered, accepting that much of it will be wasted, or (3) health care systems where a limited health care budget means that innovative, cheaper options may be the most appropriate.[22]

Table 2. Reasons and Possible Solutions for Noncompliance

| Reason for Noncompliance | Possible Solutions |
|---|---|
| Forgetting | • Reminder alarm on device<br>• Co-packaging with reminder devices such as Post-it notes or refrigerator magnets<br>• Link to cues in everyday activities |
| Administration problems | • Simple administration technique<br>• Simple patient/device interface<br>• Automatic feedback on correct and incorrect technique<br>• Notification of completion of administration |
| Effectiveness | • Will increased efficacy improve compliance? |
| Additional functions | • Monitoring of respiratory variables and feedback to patient and/or caregiver |
| Obtrusiveness | • Smaller, quieter devices<br>• Self-contained for medication and power |
| Popularity | • Popular appearance<br>• Efficient marketing |
| Cost | • Cheaper devices may be more affordable, but will they be perceived as less valuable? |

## Using Complex or Expensive Drugs to Treat Lung Disease

Inhaled medications are increasingly used to treat pulmonary illnesses other than asthma and chronic obstructive airways disease. In this review examples from pediatric and neonatal intensive care will be used to illustrate some of the drugs that may be administered by nebulizers in the future.

Table 3. Potential Therapies for Persistent Pulmonary Hypertension of the Newborn

- Inhaled nitric oxide
- Phosphodiesterase inhibition
- Magnesium
- Prostacyclin
- Partial liquid ventilation
- Surfactant

### Persistent Pulmonary Hypertension of the Newborn

Persistent pulmonary hypertension of the newborn (PPHN) has a prevalence of 1.9 per 1,000 live births,[23] and a mortality of around 11%. The illness typically occurs in term newborns and is characterized by right-to-left shunting of blood due to abnormally persistent pulmonary hypertension, leading to severe hypoxemia. Right ventricular failure occurs due to the high pulmonary vascular resistance; subsequent distention of the right ventricle impairs left ventricular function, and this reduces cardiac output. Treatment has been directed toward maintaining oxygenation and reducing pulmonary vascular resistance. Intravenous administration of vasodilators may reduce pulmonary vascular resistance but may also cause hypotension, exacerbate ventilation/perfusion mismatch, and worsen hypoxemia. Therapies such as sedation, paralysis, and mechanical ventilation are frequently used, but until recently no specific therapy had been clearly associated with reduced mortality. Table 3 lists potential therapies for PPHN.

**Inhaled Nitric Oxide.** Inhaled nitric oxide (NO) has been shown to reduce the need for extracorporeal life support in term infants with respiratory failure, including PPHN.[24] NO is a low-molecular-weight gas produced in the body by NO synthase from L-arginine. NO activates soluble guanyl cyclase, leading to an increase in cellular cyclic guanosine monophosphate (cGMP). In vascular smooth muscle cells this causes relaxation and hence vasodilatation. Inhaled NO dilates the pulmonary vessels but has no systemic hemodynamic effects because its half-life in biological tissues is extremely short. As it only dilates pulmonary vessels close to aerated lung, it improves ventilation/perfusion matching. NO is administered as a gas rather than an aerosol, and gas administration is not considered here. However, there are other therapies that act through NO. Some of these have been used experimentally or therapeutically to reduce pulmonary hypertension, and some have been, or could be, delivered via nebulization.

**Nitric Oxide Donors.** A number of drugs may act as "NO donors."[25–27] Several of these, such as sodium nitroprusside and nitroglycerin, have been used as systemic vasodilators for many years, but only recently has the administration of NO donors via inhalation been proposed.[28,29] Intrapulmonary instillation of NO donors results in selective reduction in pulmonary artery pressures and pulmonary vascular resistance, without systemic vasodilation or hypotension in animal models of pulmonary hypertension.[30,31] "Direct NO donors" are compounds that spontaneously release nitrogen monoxides, without requiring metabolism to do so, although they may require cofactors such as oxygen or thiols to facilitate NO release.[27] Other NO donors, such as the organic nitrates, require enzymatic metabolism to release NO. In the cardiovascular field there is increasing interest in linking NO donors to existing drugs for co-administration, either to reduce adverse effects or to enhance drug action. In the future such linkage may also be applied to nebulized agents used to treat pulmonary diseases.

Animal studies suggest that nebulization of a soluble NO donor can improve oxygenation and reduce pulmonary hypertension in experimental acute lung injury.[32,33] These studies support the concept that soluble NO donors may be an alternative to continuously inhaled NO gas for pulmonary vasodilation. Other substances have also shown potential as inhalable vasodilators. The NO synthase cofactor tetrahydrobiopterin has been given to healthy volunteers,[34] and several NO donor drugs have been studied in a rabbit lung preparation.[33] For pulmonary delivery, attention will focus on compounds that have reduced transepithelial permeability and limited systemic absorption, on the assumption that NO released from these compounds enters the pulmonary circulation without the parent compound, minimizing systemic adverse effects.

The half-life of inhaled NO is extremely short, so it needs to be administered continuously. Sudden cessation of administration is associated with hemodynamic instability and hypoxemia.[35] In vitro and animal data suggest that exogenous NO exposure inhibits endothelial NO synthase (eNOS) activity, and that this may be the cause of the rebound pulmonary hypertension noted after sudden withdrawal of inhaled NO.[36] There may also be a role for endothelin-1 in this phenomena, because PD156707, an endothelin receptor antagonist, blocks the rebound hypertension.[37] Oral phosphodiesterase inhibitors may be used to facilitate NO withdrawal,[38,39] but as yet there have been no controlled studies of inhaled therapy for this. The use of inhaled drugs to support NO therapy is a subject for future research.

There is also interest in slow-release NO delivery systems. A number of compounds have been produced that have promise for the regulated release of NO in nonpulmonary fields.[40–42] For instance, in cardiovascular medicine, vascular stents have been produced that slowly release NO donors.[43] NO-containing microspheres have been applied to vascular grafts, locally releasing NO over a number of days.[44] These techniques have yet to be applied to inhalation therapy.

**Prostacyclin.** The prostaglandins prostacyclin ($PGI_2$) and prostaglandin $E_1$ ($PGE_1$) are synthesized from arachidonic acid via the cyclooxygenase pathway. Both are short-acting vasodilators that cause pulmonary vasodilation in lung preparations and in animal experiments.[45,46]

Continuous intravenous prostacyclin therapy is beneficial in the treatment of patients with primary pulmonary hypertension[47] and has been suggested for the treatment of secondary pulmonary hypertension.[48] When given intravenously, however, both pulmonary and systemic vasodilation occur, leading to systemic hypotension. Also, as intravenous prostacyclin dilates vessels close to both ventilated and nonventilated lung, ventilation/perfusion mismatch may worsen, with possible impairment of arterial oxygenation.

The clinical use of inhaled prostaglandins in humans has been reported.[49,50] In patients with acute pulmonary hypertension due to acute respiratory distress syndrome, inhaled prostacyclin improves oxygenation,[50–53] causing selective pulmonary vasodilation and improved ventilation/perfusion matching, without affecting systemic blood pressure[54] or gas exchange.[55] However, systemic vasodilation could occur with prostacyclin, which is inactivated by the liver and not metabolized in the lung.[56,57] In contrast, $PGE_1$ undergoes substantial pulmonary metabolism.[58] Inhaled $PGE_1$ has been used in patients with severe multiple organ failure,[59] where it improved oxygenation but did not affect outcome. Its efficacy is similar to that of low-dose NO in reducing pulmonary artery pressures.[60]

Iloprost is a stable prostacyclin analog with strong vasodilatory[61] and antithrombotic properties.[62] Long-term beneficial effects of regular iloprost inhalations have been reported.[54,63–66] In comparison to the short duration of pulmonary vasodilation in response to inhaled prostacyclin (10–20 min), the response to nebulized iloprost lasts substantially longer (45–90 min). However, repeated administration is still necessary, and for that reason investigations are proceeding to find analogues with longer duration of action and also to assess the use of other pulmonary dilators that may have a synergistic effect (see below).

Another issue with inhaled prostacyclin is its cost, approximately £28,000 (US $45,000) per annum in the United Kingdom.[67] Devices that improve the efficiency of drug delivery will clearly be an attraction, as will the development of cheaper analogues. Selection of an efficient and appropriate drug delivery device is, of course, crucial to the success of the therapy.[68,69] In one report, failure of inhaled prostacyclin to reduce pulmonary arterial pres-

sures in a child[70] may have been due to the inappropriate choice and use of a nebulizer[71] rather than failure of the drug.

**The Role of Endothelin.** Endothelin-1 (ET-1) appears to be the final pathway for a number of pulmonary smooth muscle contractile factors. Both NO and prostacyclin inhibit the expression of ET-1. A small number of trials have been undertaken to evaluate the efficacy of oral and intravenous ET-1 receptor antagonists in pulmonary hypertension.[72–74] Future work may look at developing inhaled compounds to reduce the amounts of ET-1 with converting enzyme inhibitors or blocking the actions of ET-1 with ET-1 receptor antagonists.

**Phosphodiesterase Inhibitors.** As noted above, NO activates soluble guanylate cyclase, which in turn increases cGMP production. Smooth muscle relaxation is mediated through cGMP-dependent protein kinase. The levels of cGMP in the cell reflect a dynamic balance between production of NO by NO synthase and degradation of cGMP by cyclic nucleotide phosphodiesterases (PDE). There are at least 11 subtypes of PDE, each with its own tissue distribution and substrate specificity. $PDE_5$ and $PDE_6$ are relatively specific for cGMP. $PDE_1$ and $PDE_2$ degrade both cGMP and cyclic adenosine monophosphate. $PDE_3$ and $PDE_4$ preferentially degrade cyclic adenosine monophosphate. Drugs that inhibit PDE, particularly $PDE_5$, increase cellular cGMP, causing smooth muscle relaxation and enhancing the effect of NO. A number of these drugs are currently being investigated.

Sildenafil is a potent $PDE_5$ inhibitor that was initially used as an angina medication and has a role in the management of impotence. Because of the abundance of $PDE_5$ in the lungs it has also been used in the treatment of pulmonary hypertension.[75–78] Normally given orally, there has been one report of nebulized sildenafil use in the treatment of pulmonary hypertension in animals.[79] The advantages of the inhaled route are the minimization of systemic adverse effects and the optimization of ventilation/perfusion matching. For instance, zaprinast, an inhibitor of the cellular cGMP-selective PDE, administered intravenously caused vasodilation of poorly ventilated areas of the lung,[80,81] whereas this effect was not seen with the same drug when nebulized.[82]

PDE inhibitors may also be used to augment other therapies for pulmonary hypertension. Patients receiving inhaled prostacyclin need to undertake multiple daily treatments to achieve substantial alleviation of pulmonary hypertension. One approach to prolong and possibly increase the vasorelaxant effect of inhaled iloprost might be the concomitant use of PDE inhibitors. PDE inhibitors have been shown to prolong or augment pulmonary vasodilation from inhaled NO or prostacyclin in animal models[81,83–86] and in patients.[87] Similarly, in one study, inhalation of PDE inhibitors, nebulized in doses that caused some direct lung vasorelaxation, but that were too low to provoke systemic vasodilatory effects, led to marked augmentation of the pulmonary vasodilatory response to nebulized iloprost.[88] This enhancement of iloprost-induced pulmonary vasodilation occurred in the absence of any systemic pressure decline, and without any deterioration of gas exchange.[88] The combination of nebulized dipyridamole and iloprost has also been noted to enhance and markedly prolong the post-iloprost vasodilation.

In the management of pulmonary hypertension, therefore, a number of compounds that have shown promise in reducing pulmonary artery pressures are being developed. Delivery of these compounds via nebulization will reduce systemic effects and optimize ventilation/perfusion matching. It should be remembered, however, that pulmonary hypertension may occur in a number of illnesses seen in intensive care, and reduced pulmonary artery pressure by itself, without consideration of the underlying pathophysiologic abnormalities, may not affect outcome.

**Surfactant Therapy.** Lung surfactant is a mixture of phospholipids and proteins that reduce surface tension at the air/liquid interface in the alveolus, reducing the risk of alveolar collapse during expiration and increasing lung compliance. Surfactant also has a role in host defense and inflammation.[89] Surfactant deficiency may be primary, related to prematurity (neonatal respiratory distress syndrome or hyaline membrane disease) or to failure of functional surfactant production (ie, surfactant protein B deficiency), or it may be acquired (secondary to acute lung injury). Surfactant replacement therapy, using either artificial or animal-based surfactants, was first introduced into general clinical practice in the late 1980s and has led to increased survival and less morbidity in pre-term infants.[90,91] Studies of nebulized surfactant for acute respiratory distress syndrome have given conflicting results. One randomized study[92] showed better oxygenation with instilled or nebulized surfactant than with placebo, whereas other studies have shown no response,[93,94] though that may be due to the choice of surfactant used or the method of surfactant administration.

Surfactant is most commonly administered via direct instillation through the endotracheal tube. However, not all patients respond with sustained improvement in lung function,[95,96] possibly because of inhomogeneity of surfactant delivery in the lung, which is associated with a worse clinical response.[97] Other problems with instillation as a mode of administration include the relatively large volumes required and the large losses that occur into the oropharynx and gastrointestinal tract. Instillation normally requires temporary disconnection from mechanical ventilation, which may lead to hemodynamic instability.[98–103]

Endotracheal tube blockage has also been described following surfactant instillation. For those reasons, nebulization of surfactant has been proposed as a safer and more efficacious method of surfactant delivery.

Surfactant nebulization has been shown to lead to a more uniform distribution of surfactant throughout the lungs and to improved lung function at a much lower alveolar dose than instilled surfactant, potentially with fewer hemodynamic consequences.[104–109] However, the viscosity of surfactants make them difficult to nebulize, with bubble formation and foaming being particular problems. Also, as very little of the nebulized material is recovered from the lungs,[106,110,111] aerosol administration makes surfactant replacement more expensive and less efficacious.[111] If it is impossible to increase surfactant delivery rates with conventional nebulizers, an alternative method with a greater efficacy is needed.

Pulmonary distribution of instilled surfactant is primarily determined by gravity, and little surfactant redistribution occurs after instillation.[112] With nebulizer administration surfactant is preferentially delivered to ventilated areas of the lung, whereas it is actually needed in the nonventilated areas.[113–115] This is in contrast to the situation with the inhaled pulmonary vasodilators discussed above.

The pulmonary deposition of aerosolized surfactant is affected by the type of nebulizer and surfactant preparation used.[111] For instance, differences in protein and phospholipid content make some surfactants more viscous and hence more difficult to nebulize. This may be exacerbated by solvent evaporation, leading to increased viscosity during nebulization.

Surfactant abnormalities and deficiencies exist in a number of pediatric and adult lung diseases. Surfactant administration would seem to be an appropriate therapy, but with the exception of neonatal surfactant deficiency and meconium aspiration syndrome, replacement therapy has not consistently been beneficial. Differences in surfactant preparations are only now beginning to be understood and the importance of different constituents is being determined. For instance, the concentration of platelet activating factor differs among surfactant preparations, with high platelet activating factor levels being associated with better efficacy. Different preparations may also have different vulnerabilities to the surfactant inhibitors present in the alveoli of patients with acute respiratory distress syndrome. Improved targeting of surfactant therapy to diseased areas of the lung, by better delivery or by recirculation within the lung, could also be used to improve the efficacy of exogenous surfactant. Other strategies might include the co-nebulization of surfactant with other drugs to improve the delivery of both. Finally, nebulizers that improve the efficiency of surfactant delivery are needed before surfactant nebulization can become an accepted therapy.

### Delivery of Drugs for Gene Therapy

The development of appropriate gene delivery systems is essential for gene therapy to enter routine clinical practice.[116] Several vector systems have been proposed, including ribonucleic acid (RNA) viruses (retroviruses), deoxyribonucleic acid (DNA) viruses (adenovirus and adeno-associated virus), and nonviral systems such as cationic liposomes or naked DNA. Each of these has distinct advantages and disadvantages in terms of gene therapy.[117]

Retroviruses are RNA viruses that produce viral DNA incorporated into the host cell genome. Although they are efficient in infecting many different cell types, they can only infect replicating cells, limiting their use for in vivo treatment, because most human cells are not actively dividing. Other problems with retroviruses include the fact that the virus can only accommodate small amounts of foreign DNA, and, as the foreign DNA is inserted into the host cell genome, there is potential for oncogenesis. In contrast to retroviruses, adenoviruses can infect nondividing cells and can accommodate larger fragments of foreign DNA. However, adenoviral proteins induce a vigorous host immune response, which may invoke an inflammatory response and interfere with gene expression; that may explain the disappointing results in initial human trials that used adenovirus gene therapy for cystic fibrosis. More highly infective and less immunogenic adenoviruses have been developed, but it is not yet known whether these newly engineered viruses will be effective in gene therapy.

Nonviral vectors (ie, cationic liposomes, cationic polymers) may be used and are safer than viral vectors, but have problems gaining entry to the cell—a problem that viruses have evolved to overcome. Nevertheless, there have been a number of reports of the successful use of non-viral vectors in delivering foreign DNA to the lungs.[118–121]

Both viral and nonviral vectors can be given by nebulization. As noted with other therapies, problems to be overcome include (1) delivering the drug in sufficient quantities to the site of action, even when the airways are blocked or narrowed by disease, (2) minimizing waste and environmental contamination and improving delivery efficiency, thus minimizing drug loss and controlling costs, and (3) preventing degradation of complex molecules, such as DNA, by the nebulization process.

### Gene Therapy in the Treatment of PPHN

Infants with PPHN have low plasma concentrations of arginine and NO metabolites, suggesting that inadequate NO production may be involved in the pathogenesis of PPHN.[122] Some infants with PPHN may also have decreased eNOS expression,[123] although it is not clear if this is causally related to the development of PPHN or secondary to hypoxic stress. Studies in rats have shown some

success in delivering aerosolized recombinant adenovirus containing the ceNOS gene, leading to ceNOS immunostaining in the lungs and a rise in pulmonary cGMP levels.[124] Subsequently, hypoxia-induced increase in pulmonary artery pressures was significantly attenuated in treated animals, compared to controls.

After intratracheal lung administration of eNOS gene to mice, Champion et al found that the pulmonary vasomotor responses to bradykinin and the $PDE_5$ inhibitor zaprinast were enhanced in treated animals, but systemic responses were not altered.[125]

These studies suggest that gene therapy with the eNOS gene in vivo can selectively reduce pulmonary vascular resistance and pulmonary vascular responses to a variety of stimuli, at least in rats and mice. In the future, nebulized gene therapy may be a useful intervention for the treatment of pulmonary hypertension and other pulmonary disorders.

### Oligonucleotides and Inhalation

Antisense oligonucleotides are short, synthetic, single-stranded lengths of nucleic acid designed to induce functional gene ablation by blocking the activity of specific target messenger RNAs. They selectively bind with complementary base pairs in the target messenger RNA, preventing the formation of the gene product, and hence gene expression. The use of these antisense oligonucleotides as therapeutic agents represents an exciting challenge for the manipulation of gene expression in a variety of diseases. Problems with this technology include the high cost of the nucleotides and the difficulties of delivery to and uptake by the affected cells. This latter problem may be partly resolved in the lung by the use of nebulizer therapy. In a placebo-controlled crossover study, nebulized antisense oligonucleotides designed to target the adenosine $A_1$ receptor messenger RNA in the lung were administered to allergic rabbits. The bronchoconstrictor response to inhaled adenosine was markedly less with antisense oligonucleotides than with placebo.[126] That report raises the possibility of using nebulized therapies to directly block abnormal or undesirable gene expression in the lung.

## Summary

Advancements in nebulization technology will allow efficient, safe, and economical delivery of aerosols for gene therapy and other expensive agents, including cancer drugs, anti-inflammatories, and antibiotics. The use of nanoparticles, liposomes, and microspheres have all been described to enhance inhaled drug delivery, and improvements in formulations are anticipated as the physics of nebulization, the interaction between the drug particle and the patient, and the action of the drug at the cellular level become better understood. Most changes in nebulizer therapy will come from refining existing therapies and technologies, adapting them to suit the life and lifestyle of the patient.

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### Discussion

**Geller:** Thank you, Peter, for an excellent look into the future. I had a comment on one of your earlier points, on fashion and function. An example of that was the ultrasonic nebulizers used for high-dose tobramycin a few years ago.[1] They found that lung function went up quite a bit in cystic fibrosis patients, but it didn't catch on. Part of that might have been the expense of the drug, but the drug we have today is also expensive. I think the other part is that the ultrasonic was a big, bulky nebulizer, and it wasn't very easy to clean, use, and maintain. Inhaled high-dose tobramycin didn't catch on until it was redone in a much more user-friendly way.

Another example might be the formoterol Aerolizer in the United States. You know it's a great drug, but I don't think it's catching on very rapidly, be

cause it's in a single-use capsule powder inhaler that's not a great delivery system. I think that's a fashion statement for patients and physicians alike. So I think that *is* important.


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**Barry:** It may be that, but I see little *evidence* that's so. We may think that—I certainly think that—but there's very little trial evidence, I believe, that says that that's the case.

**Dunne:** I thought I heard you differentiate between the terms "compliance" and "adherence." Did I hear correctly? We use those terms interchangeably in the United States, and maybe we need to be a little bit more specific in our use.

**Barry:** This may be an example of our 2 nations being separated by a common language, but my understanding is that "compliance" is the number of times you actually take the medicine, compared to the number of times your physician *says* to take it. "Adherence" is the number of times you take it properly, according to the instructions of use, compared to the number of times you take it. To confuse it even more, you multiply the 2 together to get "true compliance."

**Fink:**[*] What do you see as the role of inhaled antibiotics, and where do you see them to be of value for pediatric patients such as the CF population? Is there a role for antibiotics for smaller ventilated infants?

**Barry:** Yes and no. I certainly see a role for it in my CF patients, and I regularly use it as a way of reducing intravenous antibiotic use among CF patients. We don't use it in our intensive care population. I think you have to appreciate how pseudo-scientific intensive care is sometimes. I think we're concerned, without a lot of good evidence, about the risk of antibiotic resistance in our intensive care population. The reason I'm sort of a bit embarrassed about that is because we then throw around systemic antibiotics like they're sweeties. I can't quite balance up those 2 approaches and say they're both logical, because neither of them are, I don't think. So we don't use inhaled antibiotics in the intensive care unit with the pediatric population. It may be different over here.

* James B Fink MSc RRT FAARC, Aerogen, Mountain View, California.

# Liquid Nebulization: Emerging Technologies Conference Summary

Dean R Hess PhD RRT FAARC

**Introduction**
**Why a Conference on Nebulizers?**
**Background**
**New-Generation Nebulizer Designs**
**Standardization and the Future**
**A Few Final Thoughts**

**Most physicians and respiratory therapists are knowledgeable of the use of aerosolized drugs, but many are less familiar with the performance characteristics of the nebulizer. In fact, the general opinion is that the performance of the nebulizer is relatively unimportant. However, there is accumulating evidence that the nebulizer itself does make a difference. The decision to replace a good performing nebulizer with a poor performing nebulizer may decrease the delivered dose in half or more. Although this is less important for routine bronchodilator therapy, it may make a big difference with newer aerosolized drugs. Increasingly, the Food and Drug Administration is approving drugs to be used with a specific nebulizer brand and new nebulizer designs are becoming available for use with these drugs. There are several reasons why I think this conference was important. First, new aerosol drug formulations are becoming available and these will require better performing nebulizers. Second, we as clinicians need to be knowledgeable of the newer generations of nebulizers so that we can make informed purchase decisions. Third, and perhaps most important, we must gain an increased appreciation for aerosol therapy as a science. The proceedings of this conference do much to synthesize the current state-of-the art related to new nebulizer systems. This provides, in a complete and cogent manner, the scientific basis for which clinicians can improve their knowledge of the new generation of nebulizers.** *Key words: nebulization, aerosol, jet nebulizer, ultrasonic nebulizer.* [Respir Care 2002;47(12):1471–1476]

## Introduction

The nebulizer is one of the devices most commonly used by respiratory therapists (RTs). Drugs used in nebulizers have undergone intensive scientific scrutiny, including studies of indications, hazards, complications, and treatment schedules. Many physicians and RTs are fluent in the mode of action and recommended dose of nebulizer drugs, but most are relatively ignorant of nebulizer performance characteristics. Terms such as mass median aerodynamic diameter, dead volume, and inhaled mass are just not part of the lexicon of most clinicians. Nebulizer selection is usually based on price, and the nebulizer brand may be selected by the purchasing department rather than the respiratory care department. Unfortunately, the general sentiment is that it does not matter. Contrary to the evidence, the general thinking is that the drug can be placed in any nebulizer, enough flow is added to generate an aerosol, and the patient simply breathes the aerosol for 10 minutes.

Dean R Hess PhD RRT FAARC is affiliated with the Department of Respiratory Care, Massachusetts General Hospital, and Harvard Medical School, Boston, Massachusetts.

Dean R Hess PhD RRT FAARC presented a version of this report at the 30th RESPIRATORY CARE Journal Conference, Liquid Nebulization: Emerging Technologies, held June 28–30, 2002, in Montréal, Québec, Canada.

Correspondence: Dean R Hess PhD RRT FAARC, Respiratory Care, Ellison 401, Massachusetts General Hospital, 55 Fruit Street, Boston MA 02114-2696. E-mail: dhess@partners.org.

The evidence is now clear that the nebulizer does make a difference. I published a paper more than 5 years ago that illustrated that there are considerable differences in output among commercially available nebulizers.[1] The decision to replace a good performing nebulizer with a poor performing nebulizer may decrease the delivered dose by more than half. Perhaps this does not matter for routine bronchodilator therapy, but it can make a difference with drugs that are now becoming available. In the case of tobramycin, for example, it could mean the difference between effective therapy and ineffective therapy resulting in pseudomonas infection, or the difference between effective therapy and aminoglycoside toxicity. Increasingly, the Food and Drug Administration is approving drugs for use with specific nebulizer brands, and new nebulizer designs are becoming available for use with these drugs.

### Why a Conference on Nebulizers?

Some might wonder why an entire conference devoted to nebulizers is important or necessary. In fact, some might point out that an entire conference on aerosol therapy was recently devoted to this topic.[2] There are several reasons why I think this conference was important. New aerosol drug formulations and delivery devices are becoming available. In addition to the traditional agents to treat pulmonary airway and parenchymal disease, there is a burgeoning interest in aerosol medications with pulmonary vascular effects (vasodilators),[3,4] systemic effects (insulin,[5,6] narcotics[7,8]), and genetic effects (gene therapy).[9,10] As Dr Geller pointed out in his presentation, there are 3 principal driving forces behind nebulizer innovations: (1) the ban on chlorofluorocarbon propellants commonly used in metered-dose inhalers, (2) the inefficiency of existing nebulizer designs, which is particularly an issue with new formulations, and (3) the increasing interest in using the inhalation route to deliver drugs to the circulation.

As clinicians we need to be knowledgeable about the new generation of nebulizers so that we can make informed purchase decisions. Perhaps most important, we must gain an increased appreciation for aerosol therapy as a science. As is the case in other aspects of medicine, our practice of aerosol therapy should be evidence-based. As discussed throughout this conference, there is convincing evidence that the choice of nebulizer does make a difference, particularly for newer devices and formulations.

I have often wondered why it is that, while we want evidence to support many of the therapies we use, we consider nebulizers as gadgets. We need to get away from the "bronchodilator mentality" in which the choice of nebulizer is generally considered unimportant. We need to remember that the formulation is worthless when combined with an ineffective delivery device. Perhaps this explains the failed aerosol surfactant trial for acute respiratory distress syndrome.[11,12] We need to think of the nebulizer and the formulation together as a unit, similar to the way we see metered-dose inhalers and dry powder inhalers, in which the drug and device are packaged as a single unit. As defined by Dr Dennis during his presentation, the *nebulizer* is a device (sold separately from the drug solution) that converts the liquid to aerosol droplets. The *nebulizer system*, on the other hand, includes the nebulizer, the formulation, the gas that powers the nebulizer, and the patient interface.

As clinicians we are responsible for instructing patients in the correct use of nebulizers, so we must understand how to use them effectively. As pointed out by Dr Rubin in his presentation, for nebulizer therapy to be effective the nebulizer must work well, the nebulizer-patient interface must work well, and the patient must "work well," meaning that the patient must know and use proper technique. The challenge is then to build an outstanding nebulizer that the patient will use correctly.

The presenters in this conference included many of the world's authorities on nebulizers and aerosol therapy. As seen in these conference proceedings, nebulizer designs are becoming increasingly sophisticated. To paraphrase a comment made by Dr Smaldone during the conference, we need not only *smart* nebulizers but also clinicians who are *informed* in the appropriate use of these devices. For me this conference has made many nebulizer issues less *nebulous* and has *demystified* many concepts (please excuse the puns). It is my pleasure to summarize this conference.

### Background

Dr Rau kicked off the conference with a thorough discussion of the design principles of traditional jet and ultrasonic nebulizers currently in widespread clinical use. He pointed out that many factors are known to affect jet nebulizer performance, and he distinguished between 3 jet nebulizer types: constant output, breath-enhanced, and breath-actuated (dosimetric). He also described the performance of ultrasonic nebulizers, which use a piezoelectric effect to produce aerosol.

Several important issues were discussed after Dr Rau's presentation. One was repeated nebulizer use and the resulting performance degradation. Jet nebulizers are typically designed as single-patient-use devices, but with domiciliary use the nebulizer may be cleaned and reused hundreds of times. Another issue related to domiciliary use is compressor performance. Some compressors may generate inadequate flows, and even the best performing nebulizer may perform suboptimally when used with a poorly performing compressor.

In his presentation Dr Rau presented a list of desirable characteristics for a nebulizer for clinical use. From the ensuing discussion and the subsequent presentations I gen-

Table 1. Performance Characteristics of an Ideal Nebulizer

| |
|---|
| Reliable performance: independent of fill volume, flow, power, and ventilatory pattern |
| Appropriate particle size |
| Simple to use for caregiver and patient |
| Performance independent of formulation and carrier gas |
| Operation independent of position |
| Efficient dose delivery |
| Portable |
| Multiple dose delivery |
| Easy to clean, difficult to contaminate |
| Minimal environmental contamination |
| Durable |
| Quiet, patient-friendly |
| Cost-effective |

erated a list of the characteristics of an ideal nebulizer (Table 1). However, it is important to appreciate that there are multiple trade-offs in practice and no device is likely to meet all of these criteria.

Dr MacIntyre addressed the special situation of delivering an aerosol through an endotracheal tube (ETT). As he showed, the pathway through an artificial airway is narrower than that of the native airway. However, it is well known that aerosol can be delivered through an ETT. It is generally believed that aerosol delivery through an ETT is inferior to delivery through the native upper airway, but, as Dr MacIntyre pointed out, there are few if any comparison data. Moreover, differences can be minimized by careful attention to the details of aerosol administration.

As also pointed out by Dr MacIntyre, much variability (5–40%) of dose delivery through ETTs has been reported. This is related to the many factors known to affect the delivered dose, including ventilatory pattern and timing, characteristics of the carrier gas (humidity and density), nebulizer performance characteristics, particle size, ventilator and circuit properties, and ETT size (particularly for neonates). The issue of aerosol delivery to neonates, which was raised during the discussion after Dr MacIntyre's presentation, is a special problem because of the small size of the ETT, the rapid, shallow breathing pattern, the use of ventilators with bias flow, and the use of high-frequency ventilators.

Dr MacIntyre also described a catheter device that is passed through the ETT and generates aerosol at the distal tip of the ETT, thus bypassing all of the issues related to delivering the aerosol through the ETT. The role of that device is yet to be determined. Whether it will be most useful for delivery of agents such as bronchodilators or agents such as surfactants remains to be determined.

Dr Rubin addressed issues related to the use of nebulizers in children and provided several important tips for clinical use of nebulizers in that age group. The dose of drug placed into the nebulizer should *not* be adjusted for the age of the child. He also pointed out that nebulizer therapy works best if the patient is breathing quietly (there is about 75% greater aerosol delivery if the child is breathing quietly). Dr Rubin also pleaded with clinicians to abandon the practice of blow-by aerosol therapy for infants, as this is completely ineffective.

Dr Rubin pointed out that there are a number of factors that affect patient and family compliance with nebulizer therapy, including the cost of the therapy, poor patient and family education (in which RTs can play a key role), adverse effects of the medications (eg, taste), and the time requirements for the therapy. He also indicated that a poor patient response to nebulizer therapy may be the result of prescribing the wrong drug or making the wrong diagnosis.

Professor Dolovich addressed methods to assess nebulizer performance. As she indicated, there are a number of reasons to conduct in vitro testing of nebulizers. These include testing of variability in manufacturing between units, assessing temperature changes during nebulization, assessing drug output with simulated or actual breathing patterns, and particle size characteristics of the aerosol generated. Ideally this testing should be conducted under the usual conditions of use. For complete assessment, clinical response data are necessary.

A variety of techniques have been used to assess nebulizer performance, including standing cloud measurements and unit dose collection. Particle size can be determined using a cascade impactor, laser diffraction technique, or liquid impinger. Measures of drug output from nebulizers include assessing the drug content in the aerosol, assessing the drug content remaining in the nebulizer after the delivered dose, and gravimetric techniques. If a breathing pattern is used to assess aerosol delivery from a nebulizer, this may be a simulated breathing pattern or an actual breathing pattern and may simulate a normal breathing pattern or a disease breathing pattern.

As discussed after Professor Dolovich's presentation, the principal advantage of in vitro assessments of nebulizer performance is in comparing devices. In general, in vitro models overestimate in vivo aerosol delivery to the lung. Appreciating the limitations of in vitro assessments of nebulizer performance, these are likely to continue to be important. This is particularly important as new nebulizer designs become available and their performance relative to existing devices needs to be established.

Dr O'Riordan discussed the issue of drug formulations and their effects on nebulizer performance. The formulations placed into nebulizers may be solutions, suspensions, or nanosuspensions. Characteristics of the formulation can affect nebulizer performance, even for bronchodilators.[13] Interestingly, nebulizers that perform poorly with solutions might perform better with suspensions. Characteristics of the formulation that might affect nebulizer perfor-

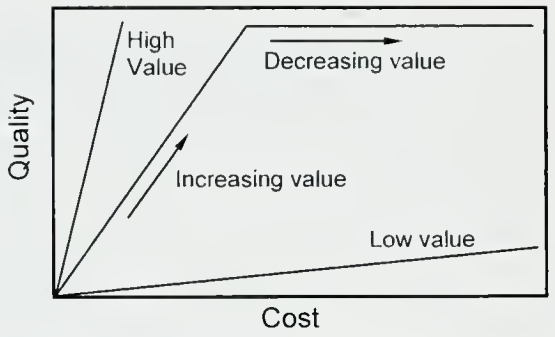


Fig. 1. Value is the relationship between quality and cost. High value occurs when quality is high and cost is low.

mance include volatility, isotonicity, and viscosity. The formulation can also affect patient tolerance, such as with alcohol versus propylene glycol solvents.

As indicated by Dr O'Riordan, there is increasing interest in delivering aerosolized liposomes into the lung, to increase nebulizer output of medications, potentially increase the residence time in the airway, and as vectors for aerosolized gene therapy. In the case of liposomes the nebulizer may affect the formulation. For example, liposomes may be affected by shear stress in a traditional jet nebulizer or heat in an ultrasonic nebulizer. As new nebulizer formulations become available, the nebulizer/formulation interaction will probably become increasingly important.

Mr Dunne addressed issues related to the cost-effectiveness of nebulizer therapy. He suggested that the principles of pharmacoeconomics can be applied to nebulizer therapy. He then described some economic analysis and its application to nebulizers, including cost-effectiveness, cost/benefit, and cost/utility. Mr Dunne suggested that there are several barriers to the clinical acceptance of a new generation of nebulizers that have a higher unit cost than currently used devices. First, traditional nebulizers are inexpensive and their limitations are accepted by clinicians. Second is the issue of caregiver indifference—the so-called "bronchodilator mentality" mentioned above.

Acceptance of a new generation of nebulizers, which are likely to have a higher unit cost than presently available devices, will challenge the provincial myopia. That is, we will need to look at the overall value of the nebulizer. Value is the relationship between quality and cost (Fig. 1). High-value nebulizers will be those that greatly increase the quality of patient care for a small increase in cost. Furthermore, cost includes more than just the price of the device. It also includes issues such as the cost of training caregivers in the use of the device, teaching patients how to use the device correctly, and the impact of the device on other important issues affecting cost, such as hospital days.

After Mr Dunne's presentation an interesting discussion ensued about caregiver protection during nebulizer therapy. This issue has generated some interest since the recognition of a higher risk of asthma among RTs, which was speculated to be due to repeated exposure to bronchodilator aerosol.[14] This concern has been more or less dismissed by RTs. There has been concern related to aerosolized pentamidine and ribavirin, and caregiver protection is recommended when those agents are administered. This concern has resurfaced with the increasing use of other aerosolized drugs, such as antibiotics. Of concern is that repeated low-level exposure to these agents could contribute to future drug resistance. There is also concern regarding the potential for exposure to other drugs under development, but the extent of that risk is not fully known. However, it seems prudent to consider caregiver exposure when nebulizers are developed for new drug formulations.

Unfortunately, Dr Robert Meyer from the Food and Drug Administration was not able to attend the conference. In his absence, the attendees discussed regulatory issues related to nebulizers. Traditionally, nebulizers and the drug formulations used in nebulizers were developed by separate manufacturers. That is quite different than the development of metered-dose inhalers and dry powder inhalers, in which the drug and delivery system is considered a drug-device combination. Increasingly, however, new drugs for inhalation are assessed as drug-device combinations. A recent example is that of nebulized tobramycin, in which the drug was approved for use with a PARI nebulizer. In the future, it is likely that new drugs for inhalation and the nebulizers used with those drugs will be assessed as drug/device combinations. This creates potential practical issues. Imagine, for example, that a drug/nebulizer combination is approved, but the drug and the nebulizer are provided by different manufacturers. What happens if the nebulizer is discontinued? Depending on the clinical importance of the drug, this could potentially have catastrophic results.

### New-Generation Nebulizer Designs

Drs Geller, Dhand, Gomez, and Smaldone described the designs and performance of the new generation of nebulizers, which was a particularly difficulty assignment because there is very little in the peer-reviewed literature describing these devices and much of what is known is proprietary. Because these devices are in various stages of development, the amount of information available in the public domain is limited. These reports presented more detailed information on these devices than is available anywhere else in the literature.

Dr Geller described systems, such as Respimat and AERx, that create aerosols by forcing pressurized liquids through orifices. Dr Dhand described systems, such as those by Aerogen and Omron, that use vibration to force liquids through multiple orifices. Dr Gomez described sys-

Table 2. Common Characteristics of the New Generation of Nebulizers

| |
|---|
| Role to be defined: bronchodilators or new formulations? |
| Efficient: large dose in small time; much larger dose than traditional nebulizer |
| Minimal dead volume |
| Independent of compressor: self-powered |
| Small and portable |
| Can nebulize a wide variety of formulations; some are formulation-specific |
| Breath-actuated |

tems that use electric fields to produce aerosols. Dr Smaldone described "smart" nebulizer designs, including the AeroEclipse, HaloLite, and AKITA. There are a number of characteristics that these devices have in common, as shown in Table 2.

In his presentation Dr Smaldone discussed the importance of matching the performance of the nebulizer to the physiology of the patient. Although this should go without saying, it occurs to me that this is not often considered when choosing a nebulizer. As clinicians we match ventilator settings to the physiology of the patient, and we match oxygen delivery devices to the physiology of the patient, so of course we should match the nebulizer to the physiology of the patient.

### Standardization and the Future

Dr Dennis discussed issues related to standardization of testing methods for nebulizers. Although such standards do not currently exist in the United States, they have been developed in Europe. The British standards were published in 1994, and the European standards were published in 2001. By and large these are type-testing standards and do not involve clinical testing. There are also European Respiratory Society nebulizer guidelines, which are evidence-based and match nebulizer output data to the drug and the patient.

As the final presentation of the conference, Dr Barry discussed the future of nebulization. He identified 3 issues that need to be addressed when developing future generations of nebulizers. We need to find ways to improve patient compliance, and unfortunately little is known today about how to do that. New formulations will be developed and we will need the appropriate nebulizers. We need to develop better nebulizers that are smaller and more portable, that provide value-added features, and that allow more precise and reproducible drug delivery. Increasingly we need to consider the nebulizer and the drug as a unit. In fact, therapy may be ineffective if a great inhalable drug is coupled with a poorly performing nebulizer.

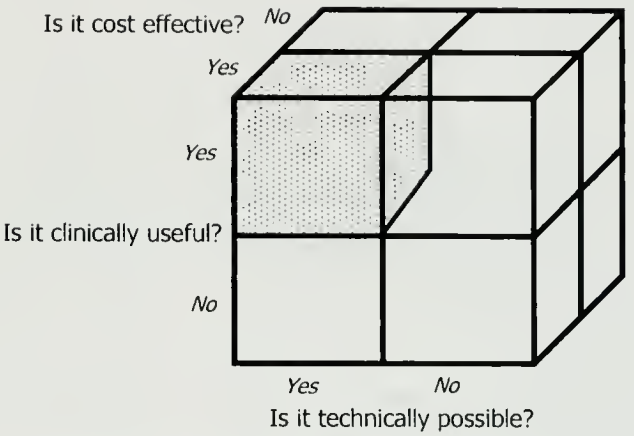


Fig. 2. Three criteria should be assessed when a new device is considered. We should adopt new technologies that are technically feasible, clinically useful, and cost-effective.

### A Few Final Thoughts

I will complete my summary by referring to a concept introduced by Dr David Pierson when he summarized a RESPIRATORY CARE Journal Conference many years ago.[15] New nebulizers will certainly be developed. As clinicians, we need to consider 3 issues related to these new devices. First, is the concept technically possible? Second, is the concept clinically useful? And, finally, is the concept cost-effective? We should adopt the use of equipment that is technically feasible, clinically useful, and cost-effective (Fig. 2).

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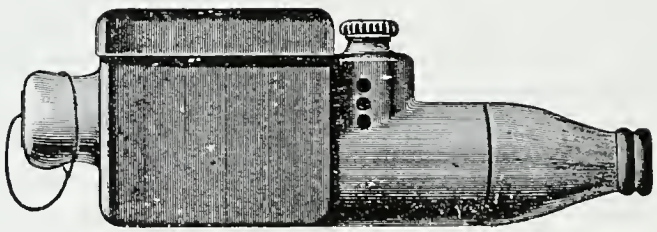

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# Books, Films, Tapes, & Software

**Respiratory Care: Principles & Practice.** Dean R Hess PhD RRT FAARC, Neil R MacIntyre MD FAARC, Shelley C Mishoe PhD RRT FAARC, William F Galvin MSEd RRT CPFT, Alexander B Adams MPH RRT FAARC, Allan B Saposnick MS RRT. Philadelphia: WB Saunders. 2002. Hard cover, illustrated, 1,289 pages, $75.

**Respiratory Care: Principles & Practice** is a substantial textbook (over 1,200 pages and 800 illustrations) for respiratory care students. The co-editors and authors represent some of the most prominent contributors to the field of respiratory care practice. The book is divided into 5 sections. Part I provides a broad foundation for our practice in its social, economic, and political context. The 7 chapters in this section describe the history of the respiratory care profession and its place within the wider critical care community. In addition, the transformation of the respiratory therapist (RT) over the past 50 years is placed within the dynamic context of an evolving (some would argue devolving) American health care system. From this follow chapters that address the wide-ranging skills required of the modern practitioner: critical thinking, ethics, communication, decision making and consulting, patient education, medical documentation, outcome assessments, health care reimbursement issues, and accessing/evaluating the medical literature.

Skills in the applied sciences that lay the foundation for respiratory care practice are treated in Part II. This includes chapters on applied mathematics, physics, chemistry, microbiology/infection control, cardiopulmonary anatomy/physiology, and pharmacology. Part III covers the broad array of assessment skills and technologies required of the RT. There are 12 chapters, which describe the physical examination and medical history acquisition, blood chemistry/hematology, arterial blood gas analysis, nutritional assessment/support, cardiac assessment, thoracic imaging, pulmonary function testing, hemodynamic and gas exchange function, exercise assessment, fiberoptic bronchoscopy, sleep assessment, and infant apnea monitoring. Part IV introduces the student to respiratory care therapeutics and covers medical gases, various forms of oxygen and aerosol therapy, secretion clearance techniques, airway management, cardiopulmonary resuscitation, adult and neonatal mechanical ventilation, noninvasive mechanical ventilation, "alternative site" mechanical ventilation, and nonconventional respiratory therapies such as nitric oxide, prone positioning, and tracheal gas insufflation.

With that groundwork laid, the final 14 chapters (Part V) cover the general principles of disease management and discuss the specific aspects of managing asthma, chronic obstructive pulmonary disease, interstitial lung disease, pulmonary vascular disease, pneumonia, cystic fibrosis, acute lung injury, postoperative respiratory complications, cardiac failure, chest trauma, burns/inhalation injuries, neuromuscular dysfunction, sleep apnea, and lung cancer.

The basic format of each chapter is designed to assist the student's task of assimilating the substantial amount of information necessary to become a competent RT. Whenever possible, topics are segmented into concise, highly focused chapters. The editors have employed various standard formatting and organizational techniques, such as providing an outline, clear learning objectives, and key terms on the first page of each chapter. A liberal use of discrete information boxes provide concise examples of complex concepts, reinforce important points made in previous sections, and summarize key points made in each chapter. New terms are always introduced in boldface for easy identification and reference. There are 3 detailed appendixes that provide a formulary of common respiratory drugs, algorithms for basic and advanced cardiopulmonary life support, electrocardiogram interpretation, and a glossary of over 900 terms. In addition, the publisher offers access to their Web site, which provides both teaching aids to instructors and links to medical-related Web sites.

In preparing this review I referred back to what I consider the gold standard of comprehensive respiratory care textbooks: *Egan's Fundamentals of Respiratory Care* (7th edition). In comparing the two books, I was very impressed with this newest offering by Hess et al. Although the general structure and content of the 2 books were similar, I personally found the specific presentation strategy of Hess et al better suited to students' needs. As an example, acute lung injury is discussed in Egan's textbook in the same chapter as cardiogenic pulmonary edema and multiple-organ system failure. Tangentially, Egan lacks a discrete chapter dealing with the critical issue of cardiac failure and its impact on pulmonary function. This results in a needlessly complicated presentation for instructors to clarify (and students to "digest"), and thus represents a pedagogic *faux pax*. In contrast, the chapter on acute lung injury in **Respiratory Care: Principles & Practice** is exceptional and effortlessly places the student within the clinical context of the disease and its management. Likewise, the chapter on cardiac failure moves smoothly from a discussion of cellular function and organ-system physics to cardiopulmonary physiology and disease management.

In general, I found the writing style in the Hess et al text more straightforward. As an example, Egan's discussion of pulmonary function testing wends its way over 2 pages toward a description of basic lung volumes and capacities by first discussing the purpose of testing, the organization of the laboratory, and the equipment. In contrast, the corresponding chapter in **Respiratory Care: Principles & Practice** begins with 2 concise introductory paragraphs. Almost immediately afterwards one finds: "A lung capacity is 2 or more lung volumes. Of the 8 lung volumes and capacities, 4 provide the most useful information." This direct writing style and straightforward presentation of material permeate the book. Do not construe my criticism to imply that the writing in Egan is poor. Rather that, from a pedagogic standpoint (given the immense amount of material that must be mastered), the respiratory care student (and instructor) is better served by writing and editing that consciously strive to lend a certain "immediacy" to the material.

When one must spend hours hovering over black-and-white text, tables, photographs, and diagrams, a subtle visual fatigue can limit study endurance. This became apparent to me by the very soothing effect that the modest application of color had on the readability of **Respiratory Care: Principles & Practice**. In general, I found

the design of tables and illustrations to be of high quality. This hard-cover book is made with high-quality paper and a strong woven binding and appears to be very durable.

In my opinion, **Respiratory Care: Principles & Practice** is intended as a challenge to Egan's status (and market share) as the preeminent comprehensive textbook of respiratory care. As such, it is modeled on a very successful formula and in some subtle but important ways has improved upon Egan. I think Hess et al should be commended for creating a worthy addition to the respiratory care literature. **Respiratory Care: Principles & Practice** should be considered seriously by educators, students, and practitioners seeking a well written comprehensive text.

**Richard H Kallet MSc RRT FAARC**
Research and Education
Respiratory Care Services
San Francisco General Hospital
University of California, San Francisco
San Francisco, California

**Long-Term Mechanical Ventilation**. Nicholas S Hill, editor. (Lung Biology in Health and Disease, Volume 152, Claude Lenfant, executive editor.) New York/Basel: Marcel Dekker. 2001. Hard cover, illustrated, 554 pages, $195.

The last 10 years have seen major progress in the management of patients on long-term ventilatory support. This has largely been due to development of noninvasive ventilation modalities that allow a greater number of patients to be treated at home. There have been a number of technical developments in the application of ventilatory support, especially with the introduction of improved ventilators for the delivery of noninvasive ventilation and improvements in the design of patient/ventilator interfaces.

Thus this book on long-term mechanical ventilation is particularly welcome and is a very up-to-date account of this rapidly developing field. The book is part of the Lung Biology in Health and Disease series and is a collection of reviews by experts on various aspects of the topic. The majority of the contributors are from North America, and this is reflected in the slant of the book, which largely reflects practice in the United States. However, there are a few chapters by European authors.

The book starts with an excellent chapter on the epidemiology of long-term ventilation and includes useful information on practice in a number of countries outside of North America, such as France, where the practice of home ventilation has been particularly well organized with the Association Fédérative Nationale pour le Traitement à Domicile de L'Insuffisance Respiratoire Chronique (ANTADIR). To date, information is available on relatively few countries, but the figures provided already show the wide variability in prevalence of patients treated outside the home. There are then 3 mainly physiologic chapters (which are excellent in content and very clearly written) on pathogenesis of chronic respiratory failure and effects on the controversial subject of respiratory muscle function. These are followed by discussion of the effects of mechanical ventilation on sleep and the upper airway. Then the book covers the various conditions that can be treated with long-term ventilatory support, and there is a particularly useful section on various neuromuscular diseases. There is brief mention of obesity hypoventilation syndrome, which is an increasing problem. The need for larger and longer-term clinical trials of noninvasive ventilatory support for patients with hypercapnic chronic obstructive pulmonary disease is stressed, as is the need to include appropriate outcomes and a health economic analysis.

In addition to the application of ventilatory support in adults, pediatric ventilatory support is increasing, and many pediatric patients will continue to adulthood and become the responsibility of adult physicians. Thus the section on pediatric issues is welcome, and it is very informative. The book continues with more practice-oriented chapters on managing invasive and noninvasive mechanical ventilation. There are some very useful pictures of available ventilators, masks, and headgear for noninvasive ventilation. This chapter also contains the best account I have read of the various complications associated with noninvasive ventilation, such as problems related to the patient interface, complications related to air pressure and flow, patient intolerance of the ventilator, air leaks, and rebreathing problems. There is also some mention of negative-pressure ventilation, though these modes of ventilation now have less importance and are used in relatively few centers in North America and Europe. Conversion from invasive to noninvasive ventilation is an important topic that is covered well, and I enjoyed reading the chapter on respiratory muscle aids and mouthpiece ventilation. A good technical chapter on ventilators includes some very clear and useful diagrams and descriptions of the more commonly used equipment. There are then chapters on health care networks and issues related to weaning from long-term ventilation and approaches to rehabilitation. The section on costs and reimbursement issues is mainly applicable to North America, but provides useful data on home care for other readers. The book concludes with 2 chapters on outcome of mechanical ventilation, the first relating to general issues such as survival and physiologic outcomes, and the last chapter describes the measurement of health status in this patient group and discusses some of the available disease-specific instruments. It is clear that future studies will need good assessment of health status as one of the primary outcome measures.

I have only a few small criticisms of the text, and one of these is the content overlap between the chapters, but such overlap is almost inevitable in a collection of reviews. Monitoring of ventilation was covered in several chapters; it could have been covered in a chapter devoted specifically to monitoring, in view of its importance in management. Similarly, health status was covered in both of the last 2 chapters, on outcomes. I was disappointed not to read more on the history of long-term ventilation, which is particularly interesting; it was only in the pediatrics chapter that a substantial amount of historical perspective was provided.

Ethical issues are becoming an increasing problem for anyone involved in managing patients on long-term ventilatory support, but this subject is addressed relatively briefly, in only a few of the chapters. A section dedicated to ethical issues would have been very welcome. In this era of increasing patient involvement in care decisions, it would have been fitting to have a chapter written by a patient, to provide the patient's perspective and requirements.

**Long-Term Mechanical Ventilation** will be of interest to anyone involved in managing patients with chronic respiratory failure requiring long-term ventilatory support, including physicians, nurses, respiratory therapists, physiotherapists, and other clinicians. The book will also be of use to providers, insurance companies, and manufacturers of ventilator equipment. The rapid developments in this field mean that the book will need updating, and another edition will need to follow. The price of the book ($195)

is relatively expensive, but I hope that it will be made available in hospital libraries, as it is a very valuable reference on an important topic.

**Jadwiga A Wedzicha MD**
Academic Unit of Respiratory Medicine
St Bartholomew's and
Royal London School of Medicine
St Bartholomew's Hospital
London, United Kingdom

**Mechanical Support for Cardiac and Respiratory Failure in Pediatric Patients**. Brian W Duncan MD, editor. Foreword by Richard A Jonas MD. New York/Basel: Marcel Dekker, 2001. Hard cover, illustrated, 369 pages, $165.

In the preface to **Mechanical Support for Cardiac and Respiratory Failure in Pediatric Patients**, Brian Duncan sets forth the goal: "to fill a void in the current literature by concisely summarizing the state-of-the-art of mechanical circulatory support for pediatric cardiac patients in a single volume." The void in current literature is real. Though there is an abundance of well-written reports, published in respected journals, of experience among practitioners at various centers, there remains a paucity of generalizable knowledge when it comes to the application of mechanical circulatory support in the nonadult population. That lack of published and generalizable information reflects the challenge Dr Duncan faced in editing this book; compared to mechanical circulatory support in the adult population, our knowledge of how to best support the failing (or failed) heart in the neonatal or pediatric patient is (please pardon the metaphor) in its infancy.

The causes of heart failure in adults are rather limited: infarction, ischemic disease, and cardiomyopathy are the usual suspects. A large number of adult patients require and receive mechanical support for failing heart, which also means there is a substantial market for the devices currently available and under investigation. That is not true of circulatory support for the pediatric population, among which the causes of heart failure are more numerous and more complex. Surgeons now surgically correct or palliate congenitally acquired diseases that many considered fatal 20 years ago. The variability of causes and effects hinders our ability to find a common approach to intervention.

Dr Duncan rises to the challenge and presents a well-written and concise summary of a moving target: the "state of the art" of mechanical support for cardiac and respiratory failure in pediatric patients. Chapters 1–14 describe all of the currently available modalities of mechanical support, including extracorporeal membrane oxygenation (ECMO), ventricular assist devices, and intra-aortic balloon pumps. The authors present practical information with a "how to" approach to initiating support and managing these patients. Chapters 15–19 discuss the future of pediatric circulatory support and describe new devices that are now or may soon be available. The final chapter, "Myocardial Remodeling and Thyroid Regulation in the Developing Heart During Mechanical Circulatory Support," by Dr Michael A Portman, is an exquisite discussion of a subject ripe for clinical research.

Though the information provided is often very technical, the perfusionist, the respiratory therapist, the nurse who functions as an ECMO specialist, and the physician with an interest in mechanical circulatory support will find the book very readable. The text includes information that is useful to respiratory therapists at the bedside as well as to perfusionists and ECMO specialists who monitor these devices. The editor dedicates one fifth of the chapters to management of the patient/device interface. The book's practical approach kept me interested for the entire book and provided insight on how to manage my own patients.

The material covered is wide ranging and includes the most common mechanisms of support; this is both a benefit and a distraction, because the various authors repeat information in some chapters. Several authors cover support using a roller pump, and several chapters cover support using a centrifugal pump. Though there are many nuances—which warrant discussion—on how different folks manage these devices, the editor should not have included repeated descriptions of how the devices work. Two chapters (16 and 18) cover the Medos ventricular assist device (one addresses experimental development of the device and one covers clinical applications), and those chapters covered much of the same information about the device. The same is true of Chapters 2 ("Centrifugal Pump Ventricular Assist Device in Pediatric Cardiac Surgery") and 8 ("Management of the Ventricular Assist Device Circuit for Pediatric Cardiac Patients").

As is true of any text that describes management techniques, one may find controversies. The chapter "The Use of ECMO for Cardiac Support in Children with Noncardiac Disease" states that "prolonged cardiac arrest requiring cardiopulmonary resuscitation for more than 5 minutes" excludes the use of ECMO. A multitude of practitioners known to me would simply not accept that assertion.

The latter controversies do not diminish the value of this text, but rather serve to underscore the need for the book and for continued dialogue and research into how best to manage these patients. The authors provide as much support as is available for their conclusions, some of it based on data from adult populations, some of it based on the personal experience of talented individuals. As most of my experience with extracorporeal support has been with roller pumps, I found the discussions of the use of centrifugal pumps and other devices enlightening. I am sure that those with similar experience with a single device will also gain a greater understanding of how other, less familiar devices can be used.

The publisher, Marcel Dekker, and the editor have produced an extraordinary book. I discovered no typographical errors, and the illustrations support and improve the understanding of the text. The references are timely, and the authors of both the chapters and the references are experts in the topics covered, which is notable in light of some authors' propensity to quote themselves extensively. Initially I thought the cost of the book prohibitive, but the information in it makes it a great investment, especially if one desires a single source of information on the state of the art of mechanical circulatory support in the pediatric population.

**Douglas R Hansell RRT**
Extra Corporeal Life Support Services
Children's Hospitals & Clinics
Minneapolis, Minnesota

**New Drugs for Asthma, Allergy and COPD**. Trevor T Hansel and Peter J Barnes, editors. (Progress in Respiratory Research, Volume 31. Chris T Bolliger, series editor.) Basel: Karger, 2001. Hard cover, illustrated, 389 pages, $245.25.

**New Drugs for Asthma, Allergy and COPD** (chronic obstructive pulmonary disease) is a masterfully crafted text with the specific aim "to offer a state-of-the-art de-

scription of the exciting progress in research and development that is being made with new therapies for asthma, allergy, and COPD." The editors, Trevor Hansel and Peter Barnes, acknowledge that much has been written on these topics and state that their intention was to "link biotechnology and the pharmaceutical industry with academic and clinical opinions." In addition, they wanted the information presented in a "concise and highly condensed" manner. The end result is a unique collection of up-to-date and (more importantly) clinically relevant information on the treatment of asthma, allergy, and COPD.

The book is a collection of 81 "ultra-concise" chapters from over 200 contributing authors from academic, pharmaceutical, and clinical settings. It addresses "every possible drug, from established, commercially available substances to compounds in their early testing phase." The book is in 14 sections, based on pharmacologic classification. For example, long-acting $\beta_2$ agonists is a subchapter within the bronchodilator section. The only exception is the first section, which is devoted entirely to general aspects of pulmonary medicine. One of the greatest challenges with the "ultra-concise" chapter format is the limited ability to adequately cover basic and, more importantly, complex topics (eg, gene therapy and therapies acting on transcription) with the appropriate amount of detail. This was accomplished in several ways. With the exception of 2 sections ("Mediator Inhibitors and Agonists," and "Protease Inhibitors"), each section begins with an overview chapter that provides background information for the upcoming section. The overview chapters are followed by specific chapters that focus on current and future medications for asthma, allergies, and COPD. Each chapter begins with a summary paragraph that helps set the stage for that chapter. Complex topics are often best described visually, and this book contains 195 color figures and 72 tables that help illustrate key points. Of note is the uniformity of figures throughout the book (eg, all the mast cells look alike). However, opportunities exist to enhance certain figures and tables. For example, tables with multiple concepts (eg, Table 2) could be more effective with distinct separation of or lines between columns and rows. Figures with multiple colors (eg, Fig. 3) could be clarified by using a color key to distinguish between treatment groups.

Each chapter is well referenced, should the reader wish to investigate topics further.

The first section is devoted to general aspects of pulmonary medicine. The "melting pot" of topics discussed includes: "The Need for New Therapy," "Current Therapy for Asthma," "Current Therapy for COPD," "Pharmacogenetics," "Delivery of Biologics to the Lung," "Immunopathology: Comparison of COPD and Asthma," "Monitoring Lung Function," "Airway Hyperresponsiveness," "Airways Remodeling," "Exhaled Breath Analysis," and "Clinical Studies on New Drugs." The concise chapter format worked well in this section, given the book's intended audience—practicing physicians. The chapter "Immunopathology: Comparison of COPD and Asthma" succinctly summarizes the often misunderstood differences between these similar yet very distinct pathologies. Sections 2–14 discuss bronchodilators, steroids, leukotriene inhibitors, mediator inhibitors and agonists, protease inhibitors, allergen- and immunoglobulin E-directed therapies, T cell immunomodulation, cytokine-directed therapy, chemokine receptor inhibition, adhesion molecule inhibitors, inhibition of cell signaling, therapies acting on transcription, and genetic therapy. Each of these broad section topics is well supported by chapters on the most current and promising future treatments for asthma, allergy, and COPD.

I think the editors met their primary objective. The primary focus is on current and future drugs for asthma, allergy, and COPD. The "ultra-concise" chapter format created a book that is useful in clinical practice because the information is current, accurate, and efficiently accessible. The plethora of figures and tables were well thought out and enhanced my understanding of the various topics. This book will be of benefit to practicing physicians, pulmonary specialists, pharmacists, respiratory therapists, and nurses with a particular interest in pharmacology.

**David Young PharmD**
Department of Pharmacy Practice
University of Utah College of Pharmacy
Salt Lake City, Utah

**Pleural Diseases**, 4th edition. Richard W Light MD. Philadelphia: Lippincott Williams & Wilkins. 2001. Hard cover, illustrated, 413 pages, $115.

The fourth edition of **Pleural Diseases**, by Richard W Light MD, is an extensive review of its topic and also a practical guidebook for pulmonologists and other physicians who take care of patients with pleural diseases. As a single-author book it reflects Dr Light's many years of clinical experience and accumulated knowledge.

The book is up to date, covering current topics such as pleural effusion in immunocompromised hosts, including human immunodeficiency virus-related diseases, pleural space lymphoma, and complications of bone marrow transplantation. The author attempts to give the reader a practical approach to patients with the pleural disease under discussion, rather than simply a summary of the evidence. There are a number of questions that remain unanswered in managing patients with pleural disease. For example, when should a chest tube be inserted for borderline parapneumonic effusion? and how should we deal with malignant pleural effusion? The author tries to provide clear answers to these difficult questions, often using algorithms. Dr Light tries to include all possible causes for pleural effusion, even extremely rare diseases such as Rocky Mountain spotted fever or atypical mycobacterial infection. In this respect the book is a sort of encyclopedia.

Chapters 1–3 cover the basics, including anatomy, physiology, and radiographic examinations. Chapter 4 deals with clinical manifestations and useful tests, reviewing pleural fluid analysis. Chapter 5, "Approach to the Patient," includes algorithms for how to work up undiagnosed pleural effusions. Chapter 6 reviews the clinical manifestations of diseases that cause transudative effusions, and Chapters 7–20 cover the clinical manifestations of diseases that cause exudative effusions. Included are metastatic malignancy, primary pleural tumor, bacterial infection, tuberculosis (TB), fungal infection, parasitic infection, viral infection, pulmonary embolism, diseases of the gastrointestinal tract, cardiac disorders, effusions encountered in obstetrics and gynecology, collagen vascular diseases, drug reactions, and miscellaneous diseases.

Chapters 21–24 are devoted to pneumothorax, hemothorax, chylothorax, and other pleural diseases, including asbestos-related disease. Procedures such as thoracentesis and pleural biopsy, chest tubes, and thoracoscopy are covered in Chapters 25–27.

If I were to offer a criticism of this book, it would be about the way the author pre-

sents the recommended approach. The approaches tend to be dogmatic. For example, regarding the role of adenosine deaminase (ADA) measurement in making a diagnosis of TB, data from many observational studies support the utility of ADA measurement for making the diagnosis of TB pleuritis. However, the evidence in those articles is not strong enough to make ADA an accepted standard. Based on what is stated in **Pleural Diseases** we can make a diagnosis of TB pleuritis if the pleural fluid ADA is $> 70$ units/L and the lymphocyte-to-neutrophil ratio is $> 0.75$. In this Dr Light may or may not be correct. My point is that we have to be mindful of the evidence behind his recommendation. The article cited for the lymphocyte-to-neutrophil ratio he used is just one among several published on that topic.

The book's hard cover is neatly illustrated with an impressive but not too vivid yellow color. The illustrations for procedures such as thoracentesis, chest tube insertion, and pleural drainage systems are excellent, being nicely drawn to facilitate understanding, especially for beginners. However, tables and figures are few and describe the basic information, such as organism isolated from pleural fluid. Only 1 color photograph figure is included, illustrating cytology. The number of radiographs included to illustrate particular diseases is smaller than I expected. The book's index is simple—just chapters and several bold subtitles—which might make this book difficult to use as a reference. However, the bibliography is extensive and includes references as recent as 2000. There are some trivial errors, including purified protein derivative $< 5$ mm for TB in human immunodeficiency virus, but I did not find any major typographical errors that might mislead readers.

Overall, this is an excellent clinical guidebook for pleural disease. I hope it will be updated frequently.

**Yoshihiro Otaki MD**
Division of Pulmonary and
Critical Care Medicine
University of Washington
Seattle, Washington

**Cystic Fibrosis in the 20th Century: People, Events, and Progress**. Carl F Doershuk MD, editor. Cleveland, Ohio: AM Publishing, 2001. Hard cover, illustrated, 417 pages, $25.95.

This fascinating book provides insight into various aspects of cystic fibrosis (CF) and the key people responsible for moving this field forward. The reader learns about the early description of CF as a distinct entity, the clinical observations during a torrid New York summer heat wave in the late 1940s that led to the finding of the sweat abnormalities and the subsequent development of the diagnostic sweat test, the discovery of the physiologic defect in epithelial electrolyte transport, and the breakthrough achievement in identifying the cystic fibrosis transmembrane regulator (CFTR) gene. The book also provides a wealth of information about the formation and growth of the Cystic Fibrosis Foundation. It describes the development of the care center network modeled after the polio treatment centers, the evolution of the patient registry, and various research initiatives of the CF Foundation, including the Research and Development Program, the Therapeutics Development Network, and the drug discovery program.

The book is in 4 sections: (1) "What Is CF, Who Has It, What Has Been Done About It? Clinical Insights and Research Progress," (2) "How Has the Community Helped with Care and Research? Volunteers Organized to Work Together," (3) "How Well Have We Done? Center Directors Remember," and (4) "Can We Do Even Better? Looking Ahead." The diverse perspectives of the authors is one of the strengths of the book, but this approach leads to some redundancy and unevenness in the quality of the chapters. Nonetheless, most of the chapters are excellent and some are outstanding. Parts of the book read like a summer novel that's too good to put down until the end of the story.

Some of my favorite chapters in the first section include:

1. The contribution from Dr Paul di Sant'Agnese, one of the "founding fathers" of CF
2. Dr Paul Quinton's description of his important scientific contributions to the field while fighting the disease himself
3. Dr Carl Doershuk's review of the Matthews Comprehensive Treatment Program, which became the blueprint for the contemporary multidisciplinary CF care model in the United States
4. Dr Mitchell Drumm's behind-the-scenes description of the discovery of the CFTR gene, and
5. Dr Philip Farrell's review of the rationale, design, and implementation of the Wisconsin neonatal screening trial

The second section of the book recounts the incredible volunteer effort that has been mounted against this disease. Many of the stories in this section are truly inspiring. The power of the individual, driven by the love of an affected child, to make a difference is captured in several chapters, including the contributions of Evelyn and Milton Graub, Doris Tulcin, Madeline and Henry Bernbaum, Phyllis and Lawson Anderson, and Robert McCreery. There are also 2 chapters in this section written by adults with CF, Bruce Baskin and Barbara Palys.

The third section of the book, a collection of vignettes from several center directors, is more variable in quality than the first 2 sections. Some of the chapters are quite interesting and others somewhat redundant. The chapter by Dr Warren Warwick describing the Minnesota experience is very informative. Unfortunately, he includes some negative comments that lead one to suspect that he does not forgive or forget past slights. This detracts from the quality of the chapter and differs from the uplifting spirit of the book as a whole.

The fourth section is very short, with only 4 brief chapters. In general this section adds little to what is covered in the previous 3 sections. However, Dr Pamela Davis brings us back to the current reality of this disease, that there is work yet to be done. She closes with this important take-home message: "Vigorous prosecution of conventional treatments should be the order of the day. Just as we cannot let up on the research to develop the cures of tomorrow, so too we cannot neglect the meticulous care of the patient today." Hopefully in future editions of the book this section can be embellished with the stories of treatments and approaches that contribute to the control, cure, and improvement in quality of life for people with CF.

Overall this book is an important contribution to what has been written about CF. I would highly recommend it to all who have any association with the disease, including patients and their families, scientists, and members of the health care team, including respiratory therapists. There is something here for everyone. All will learn, and many will find inspiration.

**Bruce C Marshall MD**
Cystic Fibrosis Foundation
Bethesda, Maryland

### Users' Guides to the Medical Literature—A Manual for Evidence-Based Clinical Practice.

(reviewed August 5–September 9, 2002)

The **Users' Guide to the Medical Literature** interactive Web site (http://www.ama-assn.org/public/journals/ughome.htm) is an on-line version of print-based editions. It is offered as a free service to subscribers of the *Journal of the American Medical Association*, and as a limited-time trial service to purchasers of either of the 2 versions of the printed manuals. The printed versions, edited by Drs Gordon Guyatt and Drummond Rennie, were previously reviewed in RESPIRATORY CARE.[1] The on-line version, edited by Dr Robert S A Hayward, and developed at the Centres for Health Evidence, University of Alberta, Edmonton, Alberta, Canada, follows the print versions exactly and offers downloadable files for each chapter. The major difference is found in the literature examples. The on-line version offers examples from current medical literature and has the ability to update or change them.

Both of the printed editions and the on-line version are derived from a series of 34 articles originally printed in the *Journal of the American Medical Association* between 1992 and 2002 and collected on-line.[2] The original articles are still available on the free Web site.

The Web site opens with 3 panels: navigator, reading panel, and work pad. A brief tour explains the function of each. The navigator has a list of headings that expand into topics such as finding evidence, process of diagnosis, and types of therapy and diagnosis. It has a familiar cascading style menu.

The navigator panel offers 2 views of the table of contents. The first is similar to the print version; the alternate view reorganizes the layout by topic, such as validity, results, and applicability. This view may be a more palatable approach for people just becoming familiar with evidence-based medicine and looking for a quick introduction to the process.

The reading panel is the equivalent of each chapter in the printed version. It displays text, graphs, and pictures related to the navigator topics. The pages are copies of the same text in the print version. Each chapter can be downloaded from the reading panel for reading off-line. This is advantageous for those not able to spend the time on-line with each chapter.

Each chapter has a work pad associated with it. The work pad, unfortunately, only works with Windows-based computers running Internet Explorer 4.0 or higher. Since this review was performed primarily on a Macintosh computer, none of the work pad features were available. During a brief foray into the Windows world, however, the work pad feature was found to provide a place to store results and other information from the papers referenced in the on-line text, as well as providing some basic statistical functions.

The work pad appears to be persistent across sessions, much like the browser cookies that remember your name when you revisit sites. Its usefulness was not readily apparent, except perhaps in association with teaching a course, where the results would be gathered and analyzed over a longer period of time.

The biggest advantage to the on-line version is the interactive way in which you can learn. For example, in Chapter 2F-5, "Economic Analysis: Finding the Evidence," the introductory paragraph describes a search process for evaluating thrombolytic agents when limited to economics, and cites an article.[3] Clicking on the reference to an article opened a pop-up window with the abstract. From there, the reader has the option of getting the full article, either through the National Library of Medicine (MEDLINE) or the original journal. If the reader has access to the on-line journal in the reference, the article can be downloaded within seconds of reading about the use of the study.

The whole process of the information cycle—assess, ask, acquire, appraise, apply—is easily grasped and reinforced throughout the Web site. It seems a much more powerful tool than reading an inert form, then trying to fumble from the book to examples in the literature to a calculator for checking statistics and then back to the book.

As noted in the review of the print versions, disclosures of potential conflicts of interest are not made within the downloadable chapters. Those who do not have the book available will probably keep the chapters individually for reference, thus not having access to that information.

A section on additional references provides many evidence-based medicine resources, both in print and on-line.

Purchasers of the printed versions of **Users' Guide to the Medical Literature** may access the service for a 60-day trial, after which the users must purchase a subscription to *Journal of the American Medical Association* or one of its affiliated journals for continued access. The cost is probably out of the range of individual respiratory therapists, but may be available through institutional subscriptions to one of the journals. As always, checking with your medical librarian should be the first step before purchasing on-line resources.

There were several technical difficulties in using the site with either the Netscape or Omni Web browser. Though the initial browser alert warns about this, it is still unreasonable to design a Web site using proprietary coding techniques that exclude users.

Despite the limited trial period and the inability to fully use the Web site on any system other than a Windows-based computer, this site offers an excellent feedback mechanism for strengthening one's abilities to effectively use evidence-based medicine. Book purchasers may not want to begin the trial period until a basic grasp of the concepts is obtained.

**Steven B Nelson MSc RRT FAARC**
Overland Park, Kansas
Mayo Pulmonary Services
Rochester, Minnesota

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# Appreciation of Reviewers

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*The Cure of Pulmonary Tuberculosis by Rest and Exercise*
Hugh M Kinghorn. Boston: R G Badger, 1924
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**Deadline for Submissions is July 21, 2003**

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**Creating a Medical Gas Management Program**
*James Webb*

**"The Family Caregiver's Role" and "My Experience Coping with Chronic Respiratory Disease"**
*Dana Wilchern Platt and David Platt*
**My Experience Working with Patients and Caregivers Coping with COPD**
*Angela King*
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**Feed Me to Death**
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*Neil MacIntyre MD*
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**Reasons and Remedies**
*Robert Kacmarek PhD*
**Patient/Ventilator Dysynchrony During Closed Loop Ventilation**
**Reasons and Remedies**
*Richard Branson*
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**Where's the Beef?"**
*Greg Spratt and James Stegmaier*
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**Therapists Sell? Sales an**
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*George Gaebler MSEd*
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*Dean Hess PhD*

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*Carl Mottram*

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## Scheduled Professor's Rounds 2003

**#1 Weaning the Long-Term Ventilator Dependent Patient** — David J Scheinhorn MD/David J Pierson MD FAARC
Live March 11; Audio April 15

**#2 Management of Pediatric ARDS** — Michael Anderson MD/Timothy R Myers RRT
Live April 8; Audio May 13

**#3 Implementing Protocols: What Have We Learned About Being Successful?** —Richard M Ford RRT FAARC/Sam Giordano MBA RRT FAARC
Live May 6; Audio June 10

**#4 Improving Patient Safety in Acute Care Hospitals: What Do Respiratory Therapists Need to Know?** — Karen J Stewart MS RRT/Kevin Shrake MA RRT FAARC
Live June 3; Audio July 8

**#5 Legal Issues That Impact the Practice of Respiratory Therapists** —Anthony Dewitt JD RRT FAARC/ Sam Giordano MBA RRT FAARC
Live August 12; Video September 16

**#6 Asthma Disease Management: What's New and How Is It Working?** — Thomas J Kallstrom RRT FAARC/Timothy R Myers RRT
Live September 9; Video October 14

**#7 Sedation and Paralysis in the Mechanically Ventilated Patient** — William E Hurford MD/Dean R Hess PhD RRT FAARC
Live October 7; Video November 7

**#8 Blood Gases: Doing It Right from Collection Through Analysis** — Carl D Mottram RRT RPFT/ Richard D Branson RRT FAARC
Live November 4; Video December 2

## Helpful Web Sites

**American Association for Respiratory Care**
http://www.aarc.org
— Current job listings
— American Respiratory Care Foundation fellowships, grants, & awards
— Clinical Practice Guidelines

**National Board for Respiratory Care**
http://www.nbrc.org

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American Association for Respiratory Care

# MEMBERSHIP APPLICATION

### *ACTIVE MEMBER*

An individual is eligible if he/she lives in the U.S. or its territories or was an Active Member prior to moving outside its borders or territories, and meets ONE of the following criteria: (1) is legally credentialed as a respiratory care professional if employed in a state that mandates such, OR (2) is a graduate of an accredited educational program in respiratory care, OR (3) holds a credential issued by the NBRC.

### *ASSOCIATE OR SPECIAL MEMBER*

Individuals who hold a position related to respiratory care but do not meet the requirements of Active Member shall be Associate Members. They have all the rights and benefits of the Association except to hold office, vote, or serve as chair of a standing committee. The following subclasses of Associate Membership are available: Foreign, Physician, and Industrial (individuals whose primary occupation is directly or indirectly devoted to the manufacture, sale, or distribution of respiratory care equipment or supplies). Special Members are those not working in a respiratory care-related field.

### *STUDENT MEMBER*

Individuals will be classified as Student Members if they meet all the requirements for Associate Membership and are enrolled in an educational program in respiratory care accredited by, or in the process of seeking accreditation from, an AARC-recognized agency.

SPECIAL NOTICE — Student Members do not receive Continuing Respiratory Care Education (CRCE) transcripts. Upon completion of your respiratory care education, continuing education credits may be pursued upon your reclassification to Active or Associate Member.

Please read the eligibility requirements for each of the classifications above, then complete the form. All information requested must be provided, except where indicated as optional. See other side for more information and fee schedule. Please sign and date application on reverse side and type or print clearly. Processing of application takes approximately 15 days.

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We request that you answer these questions in order to help us design services and programs to meet your needs.

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- ☐ Supervisor
- ☐ Diagnostic Technologist
- ☐ Instructor/Educator
- ☐ Other, specify _____
- ☐ Therapist/Technician
- ☐ Medical Director
- ☐ Student
- ☐ Staff Nurse

**Type of Business**

- ☐ Educational Institution
- ☐ DME/HME
- ☐ Home Health Agency
- ☐ Hospital/Acute Care
- ☐ Other, specify _____
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- ☐ Outpatient Clinic
- ☐ Physician office
- ☐ Skilled Nursing Facility

**Check the Highest Degree Earned**

- ☐ High School
- ☐ RC Graduate Technician
- ☐ Associate Degree
- ☐ Bachelor's Degree
- ☐ Master's Degree
- ☐ Doctorate Degree

**Number of Years in Respiratory Care**

- ☐ 0-2 years
- ☐ 3-5 years
- ☐ 6-10 years
- ☐ 11-15 Years
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- ☐ Full Time
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**Credentials**

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CHOOSE ONE LEVEL OF MEMBERSHIP

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Established to recognize the specialty areas of respiratory care, these sections publish a newsletter four times a year that focuses on issues of specific concern to that specialty. The sections also design the specialty programming at the national AARC meetings.

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A yearly subscription to RESPIRATORY CARE journal and *AARC Times* magazine includes an allocation of $11.50 from my dues for each of these publications.

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RESPIRATORY CARE

# Manuscript Preparation Guide

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The American Association for Respiratory Care and its science journal, RESPIRATORY CARE, invite submission of brief abstracts related to any aspect of cardiorespiratory care. The abstracts will be reviewed, and selected authors will be invited to present posters at the OPEN FORUM during the AARC International Respiratory Congress in Las Vegas, Nevada, December 8-11, 2003. Accepted abstracts will be published in the November 2003 issue of RESPIRATORY CARE. Membership in the AARC is not required for participation. All accepted abstracts are automatically considered for ARCF research grants.

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An abstract may report **(1) an original study, (2) the evaluation of a method, device or protocol, or (3) a case or case series.** Topics may be aspects of adult acute care, continuing care/rehabilitation, perinatology/pediatrics, cardiopulmonary technology, or health care delivery. The abstract may have been presented previously at a local or regional—but not national—meeting and should not have been published previously in a national journal. The abstract will be the only evidence by which the reviewers can decide whether the author should be invited to present a poster at the OPEN FORUM. Therefore, *the abstract must provide all important data, findings, and conclusions.* Give specific information. Do not write such general statements as "Results will be presented" or "Significance will be discussed."

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